

and screening laboratory investigations. At Princess Margaret Hospital we perform bone marrow aspirates when screening stem cell donors. Bone marrow samples are examined for morphology and hemopoietic progenitor cell reserve using colony forming unit (CFU)-GEMM assay. We report two potential donors with occult hematological malignancies on screening bone marrow aspirate. Neither patient had features of malignancy on history, physical examination or screening laboratory investigations. The first patient was a 65 year old man considered as donor for his brother with multiple myeloma. His past medical history and physical examination were unremarkable. Laboratory investigations demonstrated a normal CBC and biochemistry. A bone marrow aspirate demonstrated the presence of 12 % atypical plasma cells. Further investigations showed a monoclonal para-protein IgG kappa of 19.6 g/l. Cytogenetic analysis was normal. This was most consistent with either monoclonal gammopathy of unknown significance or smoldering multiple myeloma. CFU-GEMM assay evaluation showed 144 CFU-C, 151 BFU-E, 12 CFU-Meg and 4 CFU-GEA1A1. The second patient was a 72 year old man whose brother had chronic lymphocytic leukemia (CLL) in Richter's transformation. His past history and physical examination were unremarkable. Laboratory investigations demonstrated a normal CBC with a normal lymphocyte count. Bone marrow aspiration showed increased cellularity with 50-60% small lymphocytes. A repeat bone marrow aspirate and biopsy confirmed these findings. Flow cytometry was consistent with CLL. CFU-GEMM assay showed 50 CFU-C, 43 BFU-E, 0 CFU-Meg and 8 CFU-GEMM. Occult hematologic malignancies in these two donors were only demonstrated on bone marrow aspirates. CFU-GEMM assays showed decreased numbers of hemopoietic progenitors in both potential donors particularly in the patient with CLL. In conclusion, in view of the relatively innocuous nature of bone marrow aspiration we consider it advisable to screen particularly older stem cell donors with a bone marrow aspirate prior to donations. CFU-GEMM assays may contribute to the identification of bone marrow problems in potential donors.

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PREDOMINANCE OF RESISTANT GRAM POSITIVE ISOLATES AS SOURCES OF BACTEREMIA IN GVHD PATIENTS TREATED WITH INFILIXIMAB

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Infliximab has been evaluated as a treatment option for patients with GVHD due to its mechanism of minor necrosis factor alpha blockade. We evaluated all bacteremic episodes that occurred within 6 months of Infliximab administration in 31 patients with steroid-refractory acute GVHD between May 1999 and July 2001. Patients were treated with 10 mg/kg of Infliximab weekly for a median of 2 doses (range 1-12). All patients were receiving only steroids at the time of Infliximab, and 17 (55%) required additional salvage immunosuppressive agents. Each episode of bacteremia was defined by both clinical manifestations and microbiological documentation. Fourteen patients had a total of 21 bacteremic episodes, with a median time to infection of 84 days following the first dose of Infliximab (range 2-177 days). Five episodes were caused by multiple organisms (35%). Gram positive bacteria were isolated in 19 (90%) bacteremic episodes, and 3 (14%) of these involved multiple species. Gram negative bacteria were isolated in 3 (14%) episodes. Gram negative isolates included *Acinetobacter* (n=1), *Salmonella* (n=1), *Klebsiella pneumoniae* (n=1), and *Proteus vulgaris* (n=1). Gram positive isolates included enterococci (n=11), staphylococci (n=7), streptococci (n=2) and diphtheroids (n=2). Specific enterococcal species isolated were *E. faecium* (n=9), *E. durans* (n=1) and *E. mundii* (n=1). All but one isolate (90%) were documented as vancomycin-resistant (VRE). Staphylococcal and diphtheroid species also exhibited patterns of resistance; with 7/9 isolates reporting sensitivity to only rifampin or vancomycin. 6/14 patients (43%) died during the study period, with half of these deaths (n=3) attributable to their bacteremia. These results sug-

gest a high incidence of resistant gram positive bacteremias in patients with steroid-refractory acute GVHD treated with Infliximab. Empiric antimicrobial regimens that include agents with coverage against these types of resistant organisms should be strongly considered when treating patients in this clinical setting.

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CYTOMEGALOVIRUS (CMV) GASTROINTESTINAL DISEASE IN ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS UNDER PREEMPTIVE THERAPY BASED ON CMV ANTIGENEMIA OR POLYMERASE CHAIN REACTION

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Preemptive therapy for CMV infection/disease based on CMV antigenemia or polymerase chain reaction (PCR) has been established as the standard approach after allogeneic haematopoietic stem cell transplantation (allo-HSCT). We have evaluated the failure cases developing CMV disease, particularly gastrointestinal (GI) disease, under CMV monitoring and the following preemptive therapy. [PATIENTS & METHODS] From February, 1996 to July, 2002, 172 patients received allo-HSCT in Keio University Hospital, and all were monitored CMV reactivation by CMV antigenemia (CIO/11) and plasma real-time PCR, whose positive results were followed by preemptive therapy with ganciclovir. Among the patients, 12 patients developed histologically diagnosed CMV GI disease (upper and/or lower GI disease). All patients received allo-HSCT (related 5, unrelated 7) for hematologic malignancies, including acute leukemia (n=6), myelodysplastic syndrome (n=3), chronic myelogenous leukemia (n=1), low-grade lymphoma (n=1), and multiple myeloma (n=1). 10 patients received TBI-based regimens, and 2 received fludara-bine-based regimen for conditioning. GVHD prophylaxis was short-term MTX with cyclosporin A (n=9) or with tacrolimus (n=3). All patients developed grades II-IV acute GVHD (grade II 9, grade III 2, grade IV 1). [RESULTS] CMV GI disease developed at a median of day 31 post-transplant (range:19-120). CMV antigenemia and plasma real-time PCR did not become positive before the onset of CMV GI disease in 11 and 8 of 12 patients, respectively. Throughout the clinical course, CMV antigenemia remained at a low level in 7 of 12 patients, while CMV copy number in plasma evaluated by real-time PCR markedly elevated in all patients. [CONCLUSION¹] Pre-emptive therapy based on CMV antigenemia or PCR allows the development of CMV GI disease, since CMV antigenemia and PCR does not precede the disease development or does not precede early enough to prevent the disease development with anti-viral therapy. Furthermore, CMV antigenemia could not reflect the activity of CMV GI disease, while plasma real-time PCR could.

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PHARMACOECONOMICS OF PROPHYLAXIS FOR FUNGAL INFECTIONS IN PATIENTS UNDERGOING A HAEMATOPOIETIC STEM CELL TRANSPLANT

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BACKGROUND. A recent multi-center, blinded, randomized, head-to-head comparative study evaluated the safety and efficacy of prophylaxis in 882 haematopoietic stem cell transplant (HSCT) patients using either micafungin or fluconazole. The overall success rate for micafungin was significantly higher than the rate for fluconazole patients (80.0% vs 73.5%). The incidence of systemic fungal infections was lower for micafungin (1.6% vs 2.4%). The objective of this economic evaluation is to determine outcomes and costs associated with micafungin prophylaxis in HSCT compared to a no prophylaxis protocol. METHODS. A cost minimization study was performed to compare costs of no prophylaxis vs prophylaxis with micafungin. The analysis was conducted from

the hospital perspective of costs from hospital admission through discharge. A decision analysis model was developed to incorporate costs and outcomes associated with prophylaxis treatment success or failure, which resulted in the need for empirical therapy and developing fungal infection. Clinical outcomes for no prophylaxis were derived from a review of published literature. Clinical outcomes for prophylaxis with micafungin were based on the results of the clinical study. Published literature was used to assess hospital costs associated with HSCT patients treated with prophylaxis treatment, treated with empirical anti-fungal treatment, and with a probable or proven infection. The cost per course of micafungin was varied as part of a sensitivity analysis. In addition, sensitivity analyses were performed to evaluate the impact of all assumptions on hospital results. RESULTS. Hospital costs were \$136,000 per episode for proven/probably infection, \$91,000 for empirical therapy, and \$64,000 for no empirical therapy. The model indicated that mean total hospital costs were \$81,500 for patients with no prophylaxis compared to \$69,200 for micafungin prophylaxis. The results of the model were sensitive to assumptions about the need for empirical therapy and likelihood of developing a fungal infection. CONCLUSION. Micafungin prophylaxis in HSCT reduces hospital costs compared to no prophylaxis. Micafungin treatment reduces hospital costs due to: (1) decreased use of empirical anti-fungal therapy and (2) lower rates of probable and proven fungal infection.

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LIPOSOMAL AMPHOTERICIN B (AMB) PROPHYLAXIS IS SAFE AND EFFECTIVE IN PREVENTING INVASIVE FUNGAL INFECTIONS (IFI) IN RELATED AND UNRELATED ALLOGENEIC STEM CELL TRANSPLANTATION (ASCT)

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IFI especially with *Aspergillus* (ASG) (10-20%) is a leading cause of infectious mortality in ASCT recipients (Wingard, BBMT 5:55, 1999). Fluconazole (F) prophylaxis has been the standard approach to prevent IFI (7% failures) (Goodman et al, NEJM 326:845, 1992; Slavin et al, JID 171:1545, 1995). F is, however, ineffective against ASG IFI compared to Amphotericin B (AmphoB) or AmB. Walsh et al (NJEM 340:764, 1999) reported that AmB compared to AmphoB in pts developing fever/neutropenia (45% BMT pts) was associated with significantly fewer breakthrough IFI (3.2 vs. 7.8%, $p < 0.009$), less infusion related reactions, and less nephrotoxicity (both $p < 0.001$). We initiated a pilot study to determine the safety and efficacy of prophylactic AmB in ASCT recipients. 26 pts (29 ASCT) without previous history of IFI were given AmB (3 mg/kg/day) IV (day 0-100). Median age 8 yrs (0.5-22), 8 F, 18 M. Dx: 5 ALL (3 CR2, 2 CR3), 4 HD (2 CR2, 1 PR2, 1 PD), 2 AMI. (1 CR1, 1 Rel), 1 APL CR1, 2 NHL CR2, 3 CML, 1 Wilms' PD, 1 NBL PR, 1 Hurler's, 1 WAS, 1 HLH, 1 SAA, 1 SS, 2 Thal. 3 pts had a second ASCT for graft failure. HLA typing class A and B (serology) and class II DRBI (high resolution) were performed. Donors: 16 UCB: 4 5/6 class I, 10 4/6 (6 double class I, 4 class I/II mismatch); 9 R-PBSC (8 6/6 and 1 5/6) and 3 6/6 R-BM. 15 ASCT were myeloablative, 14 submyeloablative. GVHD prophylaxis: tacrolimus/mycophenolate mofetil (MMF) $n = 25$; cyclosporine/MMF/prednisone $n = 1$. Results: 4/29 ASCT (13%) required premedication for fever and rigors. Median follow-up is 212d (28-621d). 21% developed grade 3 elevated creatinine while 35% had correctable \geq grade 3 hypokalemia 2 to multiple nephrotoxins. No pt had AmB discontinued for toxicity. Incidence of \geq grade 2 AGVHD and CGVHD was 48% and 7%, respectively. Most importantly, despite 48% AGVHD there was only one (3.5%) documented IFI (Candida parapsilosis) and no (0%) ASG IFI. Estimated 1-yr OS is 61.5% and no deaths 2° to IFI and no evidence of IFI on 3/3 autopsies. These preliminary results suggest prophylactic AmB is tolerable and effective in preventing IFI post ASCT, especially ASG IFI. Larger randomized studies are needed to determine overall safety and long-term efficacy of this approach compared to standard prophylaxis regimens to prevent ASG IFI.

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SAFETY OF OUTPATIENT HIGH DOSE ORAL BUSULFAN IN PATIENTS UNDERGOING HAEMATOPOIETIC CELL TRANSPLANTATION (HCT)

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One hundred and fifty-four consecutive patients received a myeloablative oral busulfan (Bu) containing preparative regimen prior to HCT. Patients were screened for compliance and provided comprehensive verbal and written education prior to chemotherapy initiation. After screening, seven patients were excluded due to medication noncompliance (3), insurance requiring hospitalization (1), and hospitalization for a febrile episode (3). Following a test dose, busulfan area under the concentration curve (AUC) was measured and dosage adjustments were made to target an AUC of 1200 ng min/mL. All patients received oral anticonvulsant prophylaxis consisting of phenytoin or gabapentin. Demographics included a median age of 45 years (range 20-68 years) with 66 female and 88 male patients. Ninety-six patients underwent an autologous HCT versus 51 allogeneic HCT for the following diagnoses: 58 Non-Hodgkin's lymphoma, 12 Hodgkin's disease, 36 multiple myeloma, 23 acute leukemia, 12 chronic leukemia, and 6 other diagnoses. Preparative regimens consisted of 38 BuCy2, 106 BuCy2 and etoposide, and 3 other Bu containing regimens. Primary endpoints included number of repeat doses secondary to emesis, number of patients hospitalized secondary to oral Bu intolerance, and incidence of seizures or veno-occlusive disease (VOD). Additional Bu dosing occurred in 26 patients (17.7%) with a median of 1.5 repeated doses per patient. Five patients (3.4%) required hospitalization while receiving oral Bu. Of the 135 patients evaluated for Bu adverse events, only 2 (1.5%) experienced a generalized seizure, with one patient having a history of a seizure disorder. Based on the Baltimore criteria for VOD diagnosis, only 4 patients (3%) were determined to have VOD. with 2 patients having lymphoma involvement of the liver prior to HCT. VOD resolved in 3 patients and was a contributing cause of death in 1 patient. Following determination of the Bu test dose AUC, 82 patients required less than and 13 required more than the standard high dose Bu, 16 mg/kg based on ideal body weight. In conclusion, with appropriate selection and a comprehensive educational process, high dose oral Bu can be safely administered on an outpatient basis to patients undergoing HCT. Most patients required a downward adjustment of their Bu following determination of the AUC.

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AMBISOME® 1 MG/KG/DAY AS EMPIRIC ANTIFUNGAL THERAPY IN PATIENTS WITH PROLONGED NEUTROPENIA AND FEVER

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Empiric use of amphotericin in the setting of patients with prolonged neutropenia and fever is frequently complicated by renal toxicity. The lipid-based forms of amphotericin are associated with much less renal toxicity but are significantly more expensive than standard amphotericin B. Since June 1999 we have used Ambisome® at a dose of 1mg/kg/day as empiric antifungal therapy. We have reviewed this experience in patients who are neutropenic (ANC < 500 /mL), febrile (T > 38.0 C for > 72 hours) and on broad-spectrum antibiotics. Forty-three patients met these criteria. Of these 14 received allogeneic transplant (9 unrelated, 5 related donors) for CML (5), AML (3), ALL (1), MDS (2), MM (1); 10 autologous transplant for NHL (6), MM (3), testis (1); 18 leukemic induction and 1 high dose chemotx without transplant. All had received fluconazole prophylaxis. Twenty-seven of forty-three (63%) defervesced within 72 hours of starting Ambisome® 1mg/kg/day. Only 1/43 (2.3%) developed a positive fungal blood culture while receiving this dose of Ambisome® and that was *Candida krusei* related to an infected central venous catheter. One patient had *Fusarium* detected on bronchoscopy and expired despite dose escalation to 5 mg/kg/d. The results of this retrospective review compare favorably with trials using Ambisome® 3 mg/kg/d in this setting. At our institution a 14 day course of Ambisome® 1 mg/kg/d in a 70 kg patient costs \$976.24 compared to \$4940.60 for the same patient treated a 3mg/kg/d. While