Human Herpes Virus-6 (HHV6) in patients after Hematopoietic Stem Cell Transplantation (HSCT)

M. Hentrich, D. Oruzzo, G. Jäger, M. Schleuning, O. Stötzker, M. Schlemer, H. Kolb (Munich, D)

Objective: Latent reactivation of HHV6 frequently occurs in patients (pts) undergoing HSCT. However, its clinical relevance is still a matter of discussion.

Methods: We analysed all HHV6 positive results in pts undergoing HSCT within the BMT-unit from 1/94 to 4/00. Reactivation of HHV6 was defined either as significant increase in serum antibody titer (IgM positive, IgG > 1:64) or positive HHV-6 DNA (PCR).

Since 1/96 HHV6 DNA from peripheral blood was weekly determined from date of the pts admission until discharge as part of a surveillance program.

Results: HHV6 was reactivated in 140 pts (164 testing positive for HHV6-DNA, 10 for IgM and 14 for IgG). 132 pts received an allograft, 8 pts were autografted. The median age was 39.7 years. The diagnoses were chronic and acute myeloid leukemia (n=101), acute lymphocytic leukemia (n=12) and various hematopoietic disorders or solid tumors (n=27). Engraftment occurred at a median of 19 days, HHV6 was detected 29 days posttransplantation (median) lasting a median of 6.5 days (range 1-743). Each patient showed a median of 2 samples positive (range 1-31). HHV6 was demonstrated in peripheral blood (61%), gastrointestinal biopsies (32%), bronchoalveolar lavage (16.4%), saliva/pharyngeal fluid (18.6%), bone marrow (4.3%), lung (7.6%), liver (6.4%) and miscellaneous specimens (16.7%). Other viruses frequently observed in these pts were EBV (n=85), CMV (n=42) and Adenovirus (n=45). The majority (78.6%) suffered graft versus host disease (GVHD). HHV6 was detected before onset of GVHD in only 25/110 pts (22.8%). With regard to HHV6 40% of all pts were asymptomatic. Clinical manifestations most frequently observed included interstitial or alveolar pneumonia (23%), gastroesophageal reflux (16,5%), colitis (12,9%) and hepatopathia (7,2%). 33% of all pts were on acyclovir at time of HHV6 detection. Antiviral treatment was not successful in 27 of 41 evaluable pts under ganciclovir, 8/16 pts under foscaritine and 8/15 pts receiving cidofovir as determined by further detection of HHV6.

Conclusions: Though the high rate of viral infections must be considered we report on unusual sites of detection and HHV6-associated clinical manifestations. Antiviral therapy failed in a higher proportion of patients than expected. A study including HHV6 negative controls is ongoing.

Epstein-Barr virus load in patients undergoing stem cell transplantation

B.C. Gärtner, H. Schäfer, K. Bill, G. Eisele, N. Mueller-Lantzsch, H. Einsele (Homburg/Saar, Tübingen, D)

Introduction: Epstein-Barr Virus (EBV)-induced posttransplant lymphoproliferative disease (PTLD) continues to be a major complication following stem cell transplantation and is associated with high mortality. The aim of the study was to evaluate EBV viral load as a parameter to identify patients at risk for developing PTLD.

Methods: 68 samples of 9 patient with PTLD after allogeneic stem cell transplantation (SCT) were analyzed by quantitative competitive PCR and compared with 349 samples from 50 patients (22 children, 28 adults) without PTLD after SCT.

Results: All patients negative in EBV-DNA showed no sings of PTLD (266 samples). Patients with PTLD differed from patients without in EBV viral load. Median viral load at diagnosis of PTLD was 1 400 000 copies/microg DNA compared to 40 000 copies/microg DNA in 83 samples of patients without PTLD (p <0.0001). A cut off level of 100 000 EBV copies/microg DNA showed the best diagnostic efficacy with a sensitivity of 87% and a specificity of 91%. PTLD occurred between day 40-170 after transplantation. The median time when EBV DNA was detectable prior to clinical onset of PTLD was 36 days (range 20-71 d).

Patients developing PTLD did not differ from patients without PTLD in the time interval when the EBV viral load increased first after transplantation. EBV primary infections occurred earlier than reactivations in patients without PTLD. Peak levels did not differ between primary infections and reactivations.

Conclusion: EBV viral load is an important diagnostic tool in identifying patients at risk for PTLD. EBV reactivations or primary infections occur in a number of cases between 2 weeks and 3 month after transplantation but result only in few cases in PTLD.

Influence of human herpesvirus 6 on the in vitro expansion of cord blood CD34+ cells

J. Fleischmann, A. Nitsche, A. Radonic, W. Siegert (Berlin, D)

Human herpesvirus 6 (HHV-6), a member of the beta-herpesvirinae subfamily, is highly seroprevalent and has a world wide distribution. Two variant groups A and B are recognised. After primary infection HHV-6 persists lifelong in latency and can be reactivated in conditions of immunosuppression. It has been reported to be associated with myelosuppression after bone marrow transplantation. To elucidate the role of HHV-6 in hematopoiesis we investigated the influence of the two variants HHV-6A and B on in vitro expansion and differentiation of cord blood (CB) progenitor cells. MACS enriched CB-CD34+ cells were initially incubated with one of the HHV-6 variants and subsequently cultured for 14 days in the presence of cytokines supporting a maximal expansion of mononuclear cells. Infection was evaluated by immunofluorescence and real-time PCR. We found significant reduction of the expansion rate (p < .001) in cultures infected with HHV-6A compared to control cultures after 14 days. In contrast, HHV-6B did not exhibit a significant suppression. Inhibition affected all blood cell differentiation lines similarly as determined by flow cytometry for CD34, CD33, CD14, CXCR4 in HHV-6A, HHV-6B infected and in control cultures. Using quantitative PCR, we monitored the HHV-6 DNA load during cell culture. The correlation of cell expansion and the degree of infection (i.e. HHV-6 DNA load) revealed, that even high numbers of HHV-6A genome equivalents present in the culture had little suppressive effect on the total cell expansion. In contrast, HHV-6A had a strong suppressive effect. We were able to detect HHV-6 antigen in HHV-6A and B infected cultures but could not detect HHV-6 in immature CD34+ cells. When infection was
Haemopoietic stem cell transplantation of patients with a history of deep or systemic fungal infection

W.H. Krüger, N. Kröger, M. Abromeit, H. Renges, F. Tögel, J. Schrum, P. Schafhausen, R. Erttmann, H. Kabisch, A.R. Zander (Hamburg, D)

Patients with a positive history of systemic fungal infection undergoing allogeneic SCT are highly endangered by reactivation of their infection. For such patients some attempts of antimycotic prophylaxis with low dose conventional amphotericin-B (Am-B) have been reported. However, the major side effect of conventional Am-B is nephrotoxicity. Here, we report data of patients grafted under the protection of liposomal (lip) Am-B. 57 patients (w/m: 14/23) with a median age of 37 (2-65) years underwent allogeneic mrd (n=19), mud (n=14), syngeneic (n=2) or autologous SCT (n=2) for treatment of AL (n=24), CML (n=7), MDS (n=4), SAA (n=1), and granulomatosis (n=1). All patients had a history of fungal pneumonia with evidence for Aspergillus spp. as infectious agent in 17 cases. Three patients had suffered from Aspergillus sinusitis (n=2) and aspergillosis of the bone, respectively. Fungal infection was culture-documented in 8 cases. X-ray examination or clinical parameters led to the diagnosis in 29 cases. Therapy with Lip-AmB was started either primarily (n=18) or after a short course of conventional Am-B (n=15) or itraconazole (n=4). Lip-AmB was initiated on day +3 (-10-69) for a median duration of 18 days (2-63). The start dose of 2,7 (0,6-5) mg/kg was increased to 2,9 (1,0-8,2) mg/kg in some patients. Lip-AmB was excellently tolerated, fever and chills occurred in two patients. Creatinine showed a slight increase to 137% (85%-667%) of the base line probably not related to Lip-AmB. After a median follow-up of 28 (8-78) days 22 (60%) patients were discharged without evidence for fungal infection. 3/8 (38%) of patients with history of culture-documented mycosis died from relapse of C. krusei septicaemia (n=1), from CNS bleeding probably related to relapsed aspergillosis and from multi-organ failure without culture-proven mycosis. 5 patients have died from aspergillosis (n=2) or candidosis. One of these patients had to be grafted during active aspergillosis of the lung for disease-specific reasons. The remaining seven patients have died from multi-organ failure (n=4), GvHD and septicaemia (n=1) and pneumonia (n=2) related to bacterial infection in two cases. Patients with a history of preceding mycotic infection are at high risk to acquire potentially fatal infections under SCT. However, our data clearly show that only 7/37 (19%) of our patients developed culture-positive fungal infection during severe immunosuppression. We conclude that a history of preceding fungal infection is no contraindication for stem cell transplantation.

Prophylaxis of Toxoplasmosis (TXO) reactivation after allogeneic Stem Cell Transplantation (SCT): a prospective randomized trial comparing Trimethoprim / Sulfamethoxazole (TMP/SMX) with Pyrimethamine / Dapsone (PYR/DPS)

R. Trenschel, S. Basoglu, H.D. Ottinger, D.W. Beelen, U.W. Schaefer, V. Runde (Essen, D)

Between 1/96 and 9/98, 17 out of 270 pts manifested proven or possible TXO after allogeneic SCT. During this period 4/17 patients died from TXO as primary cause of death. Since 10/98 we started a prospective randomized monocentric study comparing TMP/SMX with PYM/DPS to prevent reactivation in patients at risk. Risk was defined as a positive serology for TXO in recipients or donors. Additionally, immunosuppression with a daily dose of more than 50 mg prednisolone was requested for inclusion. Randomization was executed when hematopoesis appeared stable at the end of hospitalization. Arm A received TMP/SMX 2 x 160 / 800 mg twice a week (A). Arm B was treated with PYM 50 mg once a week and DPS 50 mg once a day (B). Folinic acid was given 2 x 30 mg twice a week to all pts. 111/199 pts were at risk, 67/111 were randomized and evaluable. Patients with drug related side effects discontinued prophylaxis and switched to the alternative arm after resolution. During the study, 1 pt developed lethal cerebral TXO prior to randomization. The principal reason for exclusion was cytopenia (18/44 pts), immunosuppression with PDN <50mg/d (n=25), and non signed informed consent (n=1). Prophylaxis associated side effects were equally distributed in the two study arms (Fisher exact test p=0,2). Main reason for discontinuation was cytopenia. Interestingly, the covered interval by prophylaxis was significantly longer for arm A: 160 versus 67 days, respectively (t-test: p=0.001).

At a first glance, arm A seems to be better tolerated in view of the longer covered period of prophylaxis. However, longer follow up and further analysis will show whether this is due to side effects itself or to the practice of the physician to take arm B side effects more serious than those of arm A.

The influence of helicobacter pylori infection on gastrointestinal toxicity after Stx

S. Machherndl, H. Kasparu, R. Kopfmüller, J. König, O. Krieger, M. Girschikofsky, G. Schneider, D. Lutz (Linz, AT)

To evaluate the influence of the helicobacter pylori (h.p.) infection on gastrointestinal complications after high-dose chemotherapy and stem cell transplantation (STx) we tested 114 patients (54 female, 60 male) by the 13C-urea breath test prior to initiation of conditioning therapy. At the initial testing 92 patients (solid tumors: 24pts., hematological malignancies: 68 pts.) showed a negative result and 22 patients (solid tumors: 9 pts., hematological malignancies: 13 pts.) a positive result without any gastrointestinal complaints. Compared to the overall incidence of h.p. infection of 19% in these patients, the subpopulation of breast cancer-patients had a higher infection rate (41%). These 114 patients with a median age of 46 years (17-60) underwent an autologous (n=95) or allogeneic transplantation (n=19). Beside gut decontamination they all received prophylaxis with intravenous ranitidin (150mg/d) which was replaced by a proton pump inhibitor (PPI) at a dose of 40mg/d i.v. if clinical symptoms of gastritis appeared. No main differences between both
groups according to the occurrence of nausea/vomitus, enteritis and mucositis could be seen. However, the incidence of severe mucositis WHOIII/IV as well as enteritis WHO III/IV was higher in h.p. positive patients (41% and 23%) in comparison with h.p. negative patients (29% and 10%). Especially in breast cancer patients (n=22) mucositis WHOIII/IV was more pronounced in the h.p. positive group (56% vs. 15% respectively). Furthermore, the occurrence of clinical signs of gastritis could not be related to the helicobacter infection: 36% of the h.p. positive vs. 45% of the h.p. negative patients felt epigastrical pain. 88% vs.71% needed treatment with a proton pump inhibitor.

In conclusion helicobacter pylori infection seems not to influence the incidence of gastrointestinal complications but possibly the severity of mucositis and enteritis.

P542
Low-dose Amphotericin B Lipid Complex (ABLC) is safe and effective as empiric anti-fungal therapy in immunocompromised patients with hematologic malignancies

R. Powles, B. Sirohi, J. Mehta, S. Kulkarni, K. Murphy, B. Cheung, A. Conway, R. Saso, A. Riggs, S. Singhal, D. Cunningham, J. Treleaven (Sutton, UK)

ABLC (Abelcet, The Liposome Company) is a ribbon-shaped liposomal formulation of amphotericin B consisting of dimyristoyl-phosphatidylcholine and dimyristoyl-phosphatidylglycerol in a 7:3 molar ratio which is especially concentrated in pulmonary tissue. It is known to be safe and effective in presumed and confirmed fungal infections in immunocompromised patients at the dose of 5 mg/kg. There are limited data on its use at lower doses. We explored low-dose ABLC in immunocompromised patients with hematologic malignancies who had fewer of unknown origin which had failed to respond to combination antimicrobials, and were presumed to have fungal sepsis. 26 immunocompromised patients (15-70 y, median 44; 17 leukemia, 7 myeloma, 2 lymphoma) received 32 courses of ABLC at the median daily dose of 2 mg/kg rounded off to the nearest vial size (range, 1.3-2.7 mg/kg) after autologous (n=7) or allogeneic (n=8) stem cell transplantation or chemotherapy (n=17). The median neutrophil count at start of ABLC therapy was 0.1 x 10^9/L (range, 0-8.6). 14 courses of ABLC had been preceded by conventional amphotericin B and 11 by fluconazole without response. The median days of therapy with ABLC was 6 (range, 1-35). Courses of 4 doses (n=23) were considered evaluable for efficacy and all courses were evaluable for toxicity. 18 courses resulted in complete response, 3 in partial response, and 2 in failure (overall response rate 91%). The 2 failures were switched after 5 and 6 days of ABLC to 3 and 2.5 mg/kg AmBisome for 10 and 6 days respectively, grew candida and aspergillus from the sputum respectively, and died without responding. The change in serum creatinine from the beginning to the end of therapy was -56 to +54 micromol/L (median -1). 23 treatment courses had been premedicated with chlorpheniramine/hydrocortisone for the first few days. Infusion-related toxicities comprised rigors (n=9), pyrexia (n=5), hypertension (n=1), and hypotension (n=1); at least one of these toxicities was seen in 9 (28%). These data suggest that low-dose ABLC is very effective empiric anti-fungal therapy in immunocompromised patients with hematologic malignancies.

P543
Response to treatment in community respiratory viral infections in adult allogeneic bone marrow and peripheral blood stem cell transplant patients

M. Copland, W. Carman, I. Franklin, T. Holyoake, I. McQuaker, B. Jones, A. Parker (Glasgow, UK)

Viral pneumonia is an important cause of morbidity and mortality in patients undergoing allogeneic stem cell transplantation. A previous study from the USA has found viral pathogens such as respiratory syncytial virus (RSV), influenza A and B (Flu A & B), parainfluenza (Paraflu) and adenovirus emerging as significant causes of upper and lower respiratory tract infections (Clin Inf Dis 1996;22:778-82). A retrospective analysis of the incidence of community respiratory viral infections in our population was carried out for the 72 allogeneic BM and PBSC transplants performed on 70 patients between January 1997 and December 1999. RSV, Flu A & B, Paraflu, adenovirus and picornavirus were detected using direct immunofluorescence testing of nasopharyngeal aspirate or bronchoalveolar lavage fluid as clinically indicated. The overall incidence of proven community respiratory viral infection was 26% in the first year post allograft (19 of 72 transplants). These consisted of 9 cases of RSV (48%), 4 of Flu A (21%), 1 of Flu B (5%), 3 of Paraflu III (16%), 1 of adenovirus (5%) and 1 of picornavirus (5%). These results are comparable to previous US studies. Six of these 19 patients (32%) had upper respiratory signs only, 3 received specific anti-viral therapy with nebulised ribavirin for RSV (1), Paraflu III (1) and Flu A (1). The other 13 patients (68%) had lower respiratory tract signs on examination and 7 had chest X-rays changes. Of this group, 9 were treated with nebulised ribavirin for RSV (7), Paraflu III (1) and Flu A (1) respectively, and died without responding. The change in serum creatinine from the beginning to the end of therapy was -56 to +54 micromol/L (median -1). 23 treatment courses had been premedicated with chlorpheniramine/hydrocortisone for the first few days. Infusion-related toxicities comprised rigors (n=9), pyrexia (n=5), hypertension (n=1), and hypotension (n=1); at least one of these toxicities was seen in 9 (28%). These data suggest that low-dose ABLC is very effective empiric anti-fungal therapy in immunocompromised patients with hematologic malignancies.

P544
Retrospective PCR-analysis of blood samples for Varicella-Zoster Virus in stem cell transplantation

A.J. Ullmann, K. Weise, P. Brandt, C. Huber (Mainz, D)

Objective: Patients post stem cell transplantation are at very high risk for reactivating Varicella-zoster virus [VZV]. Herpes zoster infection is frequent and has the potential to disseminate. Atypical generalized zoster is associated with an increased mortality rate.

Methods: Retrospective analysis of 1282 blood samples originally collected from 53 patients for CMV-monitoring was performed. Period of analysis was approximately one year with a minimum of 6 months. Thirty-seven of the patients received an allogeneic
transplantation and 16 underwent a CD34-selected autologous transplantation. PCR-primers were selected from the ORF63 of the VZV-genome. Confirmation of the positive results was performed by southern blot analysis. The patients' histories were available from their medical record and/or telephone interview.

Results: None of the patients with negative blood PCR-results developed VZV-disease. Seven of the 12 allogeic transplanted patients with at least one positive PCR-result had a VZV-disease. Three of the positive patients developed a disseminated disease. Four of the 5 patients with a positive result and no VZV-disease received at that time point polyvalent immunoglobulins. None of the five received antiviral medications. All (n=2) of the autologous transplanted patients with a positive PCR-result developed a VZV-disease.

Conclusion: This retrospective analysis reveals that the PCR testing of the blood for VZV has a high sensitivity and suggests that a VZV-viremia occurs even during localized disease. A prospective study to evaluate the possibility to predict a disseminated VZV-disease is warranted.

P545

Antimicrobial prophylaxis in EBMT centers: a report from the EBMT infectious diseases working party

H. Akan, C. Cordonnier for the Infectious Diseases Working Party of the EBMT
(Ankara, TR; Creteil, F)

In order to know about the anti-infectious prophylactic policies used in the EBMT centers, the IDWP run a mail-in survey regarding antibacterial, antifungal, antiviral, and immunoglobulin (IVIG) prophylaxis. The survey consisted of questions on indications and modalities (drugs, doses, duration) of prophylaxis in autologous and allogeic SCT. Seventy-four centers from 18 countries responded.

1. Allogeneic transplant centers

67/71 centers give antibacterial prophylaxis during neutropenia, mostly by quinolones (58%) and 8/67 centers (12%) continue prophylaxis after the neutropenic phase, mostly until discharge. 69/73 (94%) centers give antifungals, at least during neutropenia, with fluconazole (48%), oral Ampho B (20.4%) or itraconazole (11.1%). Three centers give prophylaxis until discharge. Prolonging prophylaxis in case of GVHD is a common approach. The main selection criteria for antifungal prophylaxis are secondary prophylaxis (60%) and unrelated transplants (20%). 77/83 (93%) centers give antiviral prophylaxis during a mean duration of 90 days. 10 centers use Ganciclovir and 5 use Valaciclovir instead of Aciclovir for selected pts (unrelated SCT, CMV positivity). 25/73 (34%) centers give IVIG to all allogeic pts and half of them give 0.2-0.5 g/kg/w. 20/73 (27%) centers restrict IVIG prophylaxis to selected pts (unrelated transplants, hypogammaglobulinemia, CMV positivity).

2. Autologous transplant centers

33/37 (89%) centers give prophylactic antibacterials, mainly quinolones (67%) during neutropenia, and 6 centers continue prophylaxis after the first month. 38/42 (90%) centers give prophylactic antifungals mainly fluconazole (62%), itraconazole (14%) and oral Ampho B (12%). 45/53 (85%) centers give antiviral prophylaxis mainly Aciclovir (82%) during a mean duration of 60 days. 9/48 (18%) centers give IVIG to all pts and 11/48 (23%) only to selected pts.

Our survey indicate that although antimicrobial prophylaxis is common in SCT centers, there are great discrepancies in the policies used in the EBMT centers, with different regimens, selection criteria, and durations of prophylaxis. These findings indicate the need for guidelines. This survey will serve as a basis for future discussions and proposals of recommendations from the IDWP.

P546

Radiologically guided fine needle lung biopsies in the evaluation of focal pulmonary lesions in allogeneic stem cell transplant recipients

E. Jantunen, A. Pilonen, L. Volin, P. Ruutu, T. Parkkali, P. Koukila-Kahkola, T. Ruutu (Kuopio, Helsinki, FIN)

Lung problems are common in allogeneic stem cell transplant (SCT) recipients. We have retrospectively evaluated feasibility and usefulness of radiologically guided fine needle lung biopsies (FNLB) in the evaluation of focal pulmonary lesions in this patient population. During a 10-year period, altogether 30 FNLBs in 21 patients were performed (1-3 biopsies/patient) guided by either ultrasound (N=17) or computed tomography (N=13). The median time from SCT to the first FNLB was 131 days (20-343 d). In addition to complications of FNLB, also biopsy findings in relation to the final diagnosis were assessed. Prophylactic platelet transfusions were given in 19 procedures (66%). Complications of FNLB included clinically insignificant pneumothorax in four procedures (13%) and hemothysis in one case. The first FNLB was suggestive of invasive pulmonary aspergillosis (IPA) in six patients (29%). Additional clinically useful findings of FNLB included Pseudomonas aeruginosa (two patients) and Nocardia (one patient). The final diagnosis was IPA in 14 patients, immunological lung problems in three patients and other in four patients. FNLB is feasible in allogeneic SCT recipients with a low complication rate. The diagnostic yield is relatively high especially in suspicion of IPA. However, re-biopsy or other diagnostic methods are often needed in patients with non-confirmatory findings on FNLB.

P547

Autologous stem cell transplantation in lymphoma patients after hepatitis B reactivation: the role of lamivudine

F. Silvestri, G. Fuga, A. Sperotto, A. Ermacora, R. Fanin, M. Baccarani (Udine, I)

Among chronic carriers of hepatitis B virus receiving CHT for NHL, a reactivation of virus replication has been often observed and this may give rise to hepatitis, hepatic failure and death, and may prevent from performing further therapy including transplantation procedures.

Herein we present our experience in four patients with NHL where a hepatitis flare-up was observed after 2 (in three patients) and 6 (in one patient) cycles of standard-dose chemotherapy.
The patients were affected by mantle cell, follicle centre grade III, peripheral T-cell unspecified and diffuse large B-cell lymphoma respectively, were male aged 39, 47, 52 and 62 years respectively, HCV and HIV negative. In all patients, pretreatment HBV serology was as follow: HbsAg positive, HbeAg negative, total anti-c Ab positive, IgM anti-c negative, anti-e Ab positive and anti-s Ab negative.

Three of the patients were treated with F-MACHOP regimen, the oldest was treated with the CHOP regimen. HBV-DNA, was negative before starting chemotherapy and became positive in all four patients. After spontaneous recovery they were treated with Lamivudine 100 mg once daily and this allowed resuming and completing the chemotherapy program without another reactivation of hepatitis B.

In two patients high-dose chemotherapy and autologous stem cell transplantation was also performed under Lamivudine as a part of our program for high-risk NHL. Antiviral treatment was stopped 4 to 6 months after the last chemotherapy given.

During the follow-up period they were monitored with twice-monthly blood counts, transaminases/levels and HBV-DNA: all these parameters remained normal/negative all throughout the period. Currently, patient B.S. is in CR 19 months from diagnosis and 13 months from the end of chemotherapy; patient D.F.A. is in CR 22 months from diagnosis and 12 months from the end of chemotherapy, patient V.E is in CR 34 months from diagnosis and 26 months from transplantation; patient C.G. is in CR 23 months from diagnosis and 6 months from transplantation.

This data suggests a possible role of Lamivudine in preventing hepatitis B reactivation during administration of chemotherapy and ASCT to chronic carriers of hepatitis B virus.

P548

High incidence of invasive aspergillosis after treatment of acute GVHD with the combination of OKT3 and infliximab

J. Hahn, A. Erdmann, M. Grube, G. Hildebrandt, K. Schlottmann, R. Andreassen, E. Holler (Regensburg, D)

Background: Severe acute graft-versus-host-disease (aGvHD) of the gut is still a major complication after allogeneic stem-cell transplantation (SCT) as response rates to treatment (tx) of intestinal GvHD (iGvHD) are lower than those observed for GvHD of the skin. Since TNF-alpha (TNFa) is one of the key cytokines in aGvHD, murine monoclonal antibodies (mab) against TNFa were used in GvHD-prophylaxis and also in the therapy of severe iGvHD. Infliximab, a chimeric human and mouse mab against TNFa has been introduced recently as a new tx option for pts with progressive Crohn’s disease. This antibody showed also promising results in the tx of steroid-resistant (sr) aGvHD achieving response rates up to 80% in pts with iGvHD. In previous studies of our own, the combination of OKT3 and a murine mab against TNFa (MAK 195) showed potent synergistic effects without major side effects in the tx of pts with sr iGvHD. Thus it seemed reasonable to combine OKT3 and infliximab in the tx of severe sr aGvHD of the gut.

Results: We report the results of a pilot study using the combination of OKT3 and infliximab as second or third-line-tx in 3 pts who developed sr aGvHD grade III to IV with severe involvement of the gut after allogeneic SCT. Infliximab was given in a dose of 5 mg/kg weekly for two weeks (i.e. three doses) combined with OKT3 5mg daily for seven days. All three pts responded well showing marked improvement of diarrhea and abdominal pain. But several days to weeks after the tx all three pts died due to severe infectious complications. One patient developed histologically proven aspergillosis of the liver, in another patient invasive aspergillosis of the gut was demonstrated at autopsy and finally the third patient developed hepatic dysfunction and pneumonia which clinically presented as fungal pneumonia and of which he died despite of antibacterial and antifungal tx.

Conclusions: T cell-depletion and blocking of TNFa is an effective tx of refractory intestinal aGvHD but provokes life-threatening fungal infections. Inhibiting the inflammatory T cell response by T cell depletion and blocking the effector functions of neutrophils and macrophages by TNFa-suppression gives way to breakthrough-infections of aspergilli as could be dramatically demonstrated in our small series of three pts. We therefore conclude that pts who are really at need to receive both, T cell depleting and TNFα blocking antibodies should receive antifungal tx with substances effective against aspergilli not only in prophylactic but in full therapeutic doses.

P549

Toxoplasmosis after allogeneic bone marrow transplantation: risk factors for developing parasitemia

T.K. Held, D. Krüger, O. Liesenfeld, K. Janitschke, W. Siegert (Berlin, D)

Objective: Toxoplasmosis is a rare but serious infectious complication after allogeneic BMT. By PCR, parasitemia can be detected in the peripheral blood before symptomatic disease develops. The risk factors for reactivation of toxoplasmosis, however, are unknown.

Methods: We prospectively studied 28 consecutive patients seropositive for T. gondii with PCR at least fortnightly for the presence of T. gondii DNA in the peripheral blood. The following potential risk factors were evaluated: gender, age, type of preparative regimen (myeloablative or non-myeloablative), presence or absence of GVHD before parasitemia, receiving methylprednisolone before parasitemia, underlying disease (CML versus other malignancies), CMV reactivation, amount of specific IgG against T. gondii before BMT, and donor (family donor versus matched unrelated donor).

Results: Of the 28 patients, 8 (29%) showed T. gondii DNA in the peripheral blood at a mean of 102 days after BMT (95% CI, 30 to 173 days). Of those 8 patients, four had a persistent parasitemia which could be treated successfully in two patients. The other two patients died of fulminant toxoplasmosis despite treatment. 4 of the 8 patients demonstrated only a transient parasitemia on one or two occasions. 20 patients without parasitemia were compared to the parasitemic patients. There was no statistically significant difference between the two groups with respect to age, gender, length of follow-up, amount of specific IgG against T. gondii before BMT, preparative regimen (myeloablative versus non-myeloablative), underlying disease (CML versus other malignancies), presence of GVHD, occurrence of CMV reactivation, or donor (family donor versus MUD). Only the use of methylprednisolone was observed more frequently in patients with T. gondii parasitemia (7 of 8 patients) versus the control group (10 of 20 patients); this, however, just missed statistical significance (p = 0.07 by the Fisher exact test).

Conclusions: In this series of patients, no risk factor for T. gondii parasitemia could be detected. Until a population at risk can be identified in larger series, regularly monitoring allogeneic BMT patients seropositive for T. gondii may be justified for the presence of T. gondii DNA, especially if the patients receive steroid medication.
Amphotericin B Colloid Dispersion (ABCD) for the treatment of proven or presumed fungal infections in immunocompromised patients with hematologic malignancies

B. Sirori, R. Powles, S. Kulkarni, R. Pinkerton, S. Meller, K. Murphy, A. Wilgress, A. Conway, C. Seydel, J. Mehta, S. Singhal, J. Treleaven, D. Cunningham (Sutton, UK)

ABCD consists of amphotericin and sodium cholesteryl sulfate in a 1:1 molar ratio. Between 7/99 and 7/00, 58 immunocompromised/neutropenic patients (2-71 y, median 48) with hematologic malignancies (31 acute leukemia, 16 myeloma, 4 lymphoma, 7 other) received 65 courses of ABCD at daily dose of 1 mg/kg for presumed (n=55) and 3-4 mg/kg for proven/strongly suspected (n=9; 3 microbiologic, 6 radiologic) fungal infections. ABCD administration followed allogeneic (n=14), autologous (n=17), or syngeneic (n=2) stem cell transplantation, or chemotherapy (n=32). The major indications for the use of ABCD were renal dysfunction or potassium requirements >3 mmol/kg/d on conventional amphotericin. In view of known problems with infusion-related toxicity of ABCD, each dose was administered over 4-6 h after premedication comprising 1 g paracetamol, 10 mg chlorpheniramine, 25-50 mg pethidine, 100 mg hydrocortisone and 20 mg nefopam in various combinations. Courses comprising 4 doses were evaluable for efficacy, and all courses were evaluable for toxicity. The median neutrophil count at initiation of treatment was 0 and the median baseline creatinine was 141 micromol/L (18-460). 46 courses in 43 patients (4-26 doses, median 9) were evaluable for efficacy. 9 courses in proven infections resulted in 2 complete and 4 partial responses, and 3 failures (67% response). 37 courses in presumed infections resulted in 23 complete and 4 partial responses, and 10 failures (73% response). The overall response rate was 72%. The change in serum creatinine from the beginning to the end of therapy was -145 to +33 micromol/L (median -27). Despite premedication, significant infusion-related toxicity was seen: 30 (46%) rigors, 26 (40%) pyrexia, 6 (9%) bronchospasm, 6 (9%) rash, and 4 (6%) anaphylaxis. At least 1 of these toxicities was seen in 37 (57%). Tachypylaxis developed to infusion-related reactions with subsequent doses. 12 (18%) patients experienced hepatotoxicity which could not be definitely attributed to ABCD. The underlying intervention (type of transplant or chemotherapy) did not affect efficacy or toxicity. We conclude that despite its toxicity, the high incidence of infusion-related side effects seen in ABCD-treated patients despite extensive premedication is likely to be a limiting factor in the usefulness of this drug. The frequent use of corticosteroids mandated by ABCD may be detrimental in patients who are already immunocompromised and/or neutropenic.

Prospective peripheral blood PCR screening of HHV-6 in allogeneic transplant patients

C. Jacquy, M. Aoun, J. De Bruyene, V. Duchateau, P. Martiat, F. Crockaert, D. Bron (Brussels, B)

Human Herpes Virus 6 (HHV-6) is ubiquitous through the human population, with more than 80% of adults being sero-positive. The incidence of HHV-6 reactivation and its impact on morbidity in allografted recipients is poorly known. We have conducted in the last six months a prospective PCR screening of HHV-6 in 20 consecutive patients allografted in our institution (6 CML, 1 CLL, 1HD, 4 AML, 7 ALL, 1 MDS) with 14 HLA-identical (10 related and 4 unrelated) and 6 haplo-identical donors. Acyclovir was used in all as prophylaxis.

PCR screening for HHV-6 was performed twice a week on peripheral blood (PB) and on bone marrow or organs biopsies (liver, gut or skin) when available. A nested PCR using primers recognizing type A and B HHV-6 early antigen gene was used. Out of the 20 patients, five became PCR-positive, four of which displayed clinical symptoms. P1 (matched unrelated T-cell depleted transplant) engrafed normally, with grade II skin GVHD after the second DLI. HHV-6 was initially detected in a liver biopsy (day 23) performed for hepatitis associated with viral encephalopathy. He was first successfully treated with foscavir but reactivated 7 months later with the same clinical pattern. P2 (T-cell depleted haplo-identical transplant) engrafed normally without aGVHD. We was successfully treated with foscavir after detection of HHV-6 in PB at month 1 associated with encephalopathy confirmed by MRI. At month 3, PCR became positive again in PB and marrow without clinical symptoms and it was decided not to treat. P3 (matched related transplant) engrafed normally, and developed limited cGVHD after early cyclosporin withdrawal for lack of molecular response. He presented with mild hepatitis at month 4. A liver biopsy was performed and revealed positive for HHV-6, with marrow and PB screening remaining negative throughout the follow-up. Foscavir treatment led to resolution of hepatitis. P4 (matched related transplant), engrafed normally without GVHD. He then became PCR positive for both CMV and HHV-6 in PB and marrow and was treated with ganciclovir with negativation of both PCR tests. We conclude that HHV-6 reactivation may be an underestimated factor of morbidity in allogeneic transplant and should therefore monitored carefully. However, PCR screening in PB does not appear as a sensitive marker as in CMV reactivation, some patients showing positivity only in the involved organ tissue and the role of PB PCR screening remains to be better defined.

Clearance of candida albicans from kidneys of immunocompetent (IC) and Immunosuppressed (IS) mice following intermittent treatment with high dose AmBisome (AmBi)

J. Olson, J. Adler-Moore (Pomona, USA)

Systemic candidiasis is difficult to completely eradicate using conventional treatment regimens, especially in continuously suppressed animals. It was hypothesized that with the unique pharmacokinetics of AmBi (i.e., sustained bioavailability in tissues and reduced toxicity at high doses), an intermittent, high dose treatment regimen could be designed that would be effective in clearing the infection from the kidneys of both IC and IS Candida albicans infected mice. By monitoring the kidneys for clearance at various times during treatment, it could also be determined if the immune status of the animals effected the length of treatment needed. Groups of IC or IS mice (cyclophosphamide 75 mg/kg IP, 2X/wk throughout study)(n=20/group), were challenged IV with 5.9 Log CFU (IC) or 4.8 Log CFU (IS). Beginning d2 post-challenge, IC or IS mice received IV, either 20 mg/kg AmBi or 5% dextrose, 3X/wk. After 1, 3 or 5 weeks of treatment, the amount of Candida in the kidney tissue was assessed 48h post-treatment. An additional five IC and IS mice received no further treatment after wk 5. At the end of wk 9, their kidneys were examined for the presence of fungi. Both IS and IC mice had a dose dependent, significant (p<0.05) reduction in median
Detection of early stage pulmonary aspergillosis by combined ELISA assay and chest CT scan

D. Mattei, N. Mordini, A. Gallamini, R. Ghirardo, M. Ferrua, M. Osenda, C. Viscoli (Cuneo, Genoa, I)

Introduction: the diagnosis of Invasive Aspergillosis (IA) in neutropenic patients affected by hematological neoplasms is cumbersome, due to the difficulty of obtaining adequate biopsy and cultural specimens, very scarce results of radiological detection of early lesions, inadequate results of serologic tests. RT-PCR detection of DNA is still under study, and detection of galactomannan by ELISA is sensible, but not particularly specific.

Patients and methods: we performed 263 seriated ELISA assays twice a week in 37 autoalloBMT and neutropenic patients at risk for invasive mycoses (neutropenia, GVHD, high-dose chemotherapy, immunosuppressive treatment): 6 alloBMT (3 ANLL, 2 MM, 1 BC CML), 16 autoBMT (8 MM, 6 NHL, 2 HD), 8 ANLL, 2 SAA, 2 BC/AP CML, 1 CLL, 1 HD, 1 NHL. Antifungal prophylaxis included fluconazole, itraconazole or i.v. low-dose amphotericin B (Am-B). The results of ELISA assay was considered positive in a single patient, if at least two consecutive positive tests were obtained. All febrile patients entered a program of radiological survey by weekly chest CT scan.

Results: 241 assays out of 263 were negative. There were 19 positive results for 9 affected (positive) patients, developing IA as follows: 2 proven cases, and 7 probable according to the revised EORTC Mycoses Study Group criteria; in all the patients positivity of ELISA assay was sustained and durable, and increased with the efficacy of antifungal treatment. At the onset of ELISA assay positivity the chest RX was negative; while the chest CT scan detected only subtle pulmonary changes, suggestive of fungal lesions, and thereafter became diagnostic of IA. The remaining 28 patients (including 2 with borderline single positive assay and one with only a single positive test) never developed IA. Sensitivity and specificity of ELISA assay (considering proven and probable IA diagnoses) were 100%. At onset of ELISA assay positivity the patients were given 1-1.5 mg/kg/day Am-B, eventually changed to 3-5 mg/kg/day liposomal Am-B. In 2 ANLL patients, refractory to liposomal Am-B, voriconazole determined improvement of pulmonary cavitations in 1 and regression in the other patient, enabling him to undergo alloBMT. Mortality was high, reaching 50% in alloBMT and 12.5% in autoBMT recipients.

Conclusion: we suggest that combination of routine, twice a week, ELISA assay and weekly chest CT scan could enable an early diagnosis of pulmonary IA, for targeted antifungal treatment.
Respiratory virus infections in adult T-Cell depleted allograft recipients: risk factors and response to anti-viral therapy

S. Chakrabarti, K. Collingham, K. Holder, C. Fegan, T. Gentle, D. Milligan (Birmingham, UK)

We prospectively evaluated respiratory virus infections in 40 allograft recipients conditioned with conventional myeloablative (n=23) or non-myeloablative treatment and T-cell depleted with Campath antibodies. Throat samples were obtained weekly for 180 days. Upper and lower respiratory symptoms were evaluated by naso-pharyngeal aspirates and BAL. Parainfluenza (PIV), RSV, Influenza (IFA) and adenovirus infections were treated with ribavirin (oral, inhaled or IV) in a dose escalation regimen. IFA infection responded to treatment with amantadine or zanamivir if unresponsive. 16 episodes of respiratory virus infection were detected in 9 patients (22%). All infections were associated with upper respiratory illness and 5 had lower respiratory involvement. PIV3 (PIV3; 5, PIV1; 1), and RSV(5) were the commonest isolates. There were four episodes of influenza (IFA 3; IFA 1) and 2 episodes of rhinovirus and a single episode of adenovirus. Eighty one (66%) had aspergillosis, 35 (29%) candidiasis and 6 (5%) another IFI. According to the criteria of the EORTC/MSG, aspergillosis was retrospectively graded as “proven” in 17% of the cases, as “probable” in 62% and as “possible” in 21%. The duration of treatment ranged from 7 to 48 days (median 23 days). Two episodes of rhinovirus and one of IFA were self-limited and were not treated with antivirals. The adenovirus infection responded to donor lymphocytes. Two patients each with PIV and RSV required oral or iv ribavirin at 60 mg/kg/day. The 3 other episodes of PIV and 2 episodes of RSV responded to inhaled ribavirin. IFA infection responded to amantadine in one patient and another patient needed zanamivir. There was one death (11%) related to respiratory virus infection (RSV and IFA). On analysis of the risk factors, the dose of Campath antibody was the only significant factor (7 infections in 18 patients receiving 100mg Campath versus 2/22 in patients receiving a lower dose p=0.03, OR 4.5 (1.1-26). On comparing the immunological recovery, the median CD4 cell count at 3-6 months was lower in the infected group (72±45/mm3), compared to the non-infected group (186±72/mm3); p=0.003. In conclusion, multiple respiratory virus infections are frequent after T-cell depleted transplants, the dose of T-cell antibody being a significant risk factor. Infection correlated with a poor CD4 recovery at 3-6 months post-transplant. Although mortality was low, prolonged antiviral therapy added to the morbidity and cost.

Screening for Aspergillus spp. by a PCR of whole blood samples from patients with haematological disorders

C. Lass-Flo¨rl, E. Gunsilius, D. Nachbaur, H. Einsele, M. Dierich (Austria, Germany)

We performed a screening for Aspergillus spp. by polymerase chain reaction of whole blood samples in patients with haematological disorders. In a two-year study, 121 patients admitted to the University Hospital of Innsbruck for cancer chemotherapy without clinical signs of fungal infection were prospectively screened for Aspergillus spp. In 28 of 121 (23%) patients Aspergillus DNAemia was detected. Of these patients 16 (57%) were positive only once for Aspergillus DNA but positivity was never associated with invasive aspergillosis. PCR positive episodes were short and resolved without antifungal treatment. Five patients (18%) had intermittent PCR positive results. Seven (25%) patients presented at least two consecutive positivity was never associated with invasive aspergillosis. PCR positive episodes were short and resolved without antifungal treatment. Fifty six percent of the aspergillosis and 70% of the candidiasis were treated with more than 2 lines of antifungal treatment. First line treatments were amphotericin B (44%), azoles (16%), amphotericin B mixed in Intralipid (16%), liposomal amphotericin B (11.5%), lipid complex of amphotericin B (5%) with a cure rate of 42%, 43%, 25%, 44% and 15% respectively. In haematopoietic stem cells transplant recipients, antifungal first line treatments were 31%, 22%, 8%, 22% and 6% respectively. The overall mortality rate was 52 % and was higher in aspergillosis (56%) than in candidiasis (45%). Death was attributed to the IFI in 67% of the aspergillosis and in 28% of the candidiasis. In transplant patients, cure rate was 41 % and an overall mortality was 58 %. In conclusion, this first pharmaco-epidemiological study evaluates the incidence of IFI in haematology departments in France and reflects the variety of treatments used as first line antifungal therapy.
Use of intravenous cidofovir for the treatment of adenovirus infection in pre/post bone marrow transplant patients

G. Nebbia, F.M. Mattes, M. Potter, H.G. Prentice, M. Ethell, P.D. Griffiths (London, UK)

The overall incidence of adenovirus infection following bone marrow transplant (BMT) has been reported in two comprehensive studies at 5% and 21%, with rates of disease of 1% and 6.5%, respectively. The clinical manifestations of adenovirus infection in BMT recipients range from fever with gastroenteritis or cystitis to disseminated disease with multi-organ involvement and high mortality. Although there are several case-reports which support either the use of ribavirin with or without immunoglobulins, or cidofovir, no conclusive evidence of benefit has been defined. The antiviral agent cidofovir (IS)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine, HPMPC) is an acyclic nucleoside phosphate with broad-spectrum activity in vitro against several DNA viruses, including adenovirus. We report the use of intravenous (iv) cidofovir for the treatment of adenovirus infection from June 1999 to October 2000 in five haematology patients: four children and one adult (age range: 3 years -29 years). In four patients, the infection occurred post-allogeneic transplantation (3 HLA-identical related; 1 haplotype mismatched) between days +22 and days +123; one patient had adenovirus infection before transplantation. In three patients, adenovirus was isolated only from faeces, but two patients had disseminated infection with isolates from multiple sites (oropharynx, urine, faeces, and conjunctiva). All patients received iv cidofovir at a dose of 5 mg/kg once a week (and thereafter every fortnight) for at least 2 weeks or until negative for adenovirus by viral culture. Four patients cleared adenovirus within one month after commencing treatment and one patient died because of a fungal infection while still on cidofovir, and no follow-up sample was available. Cidofovir was well tolerated, and no severe side effects were observed. Conclusion: Cidofovir has been used for the treatment of adenovirus infection in pre-/post-BMT patients. Based on these preliminary results further randomised/multicentre studies are warranted to establish the efficacy of cidofovir in the treatment of adenovirus infection.
Infectious complications in 166 patients with breast cancer treated with high-dose chemotherapy and autologous peripheral stem cell transplantation

J.C. Torrego, L. Vázquez, D. Caballero, M.I. González-Fraile, M.C. del Cañizo, J.A. Pérez-Simón, C. López, R. Hernández, C. Rodríguez, A. Gómez-Bernal, J.F. San Miguel, J.J. Cruz (Salamanca, E)

There are few studies which determine the overall incidence and main types of infectious complications in patients with solid tumors undergoing autologous transplantation.

PURPOSE: To define the incidence and types of infections occurring during the first thirty days after autologous peripheral stem-cell transplant, and establish the pattern of empirical chemoprophylaxis used.

PATIENTS AND METHODS: From January 1994 to December 1999, 166 women with a median age of 46 years (21-60) diagnosed of breast cancer were treated with autologous peripheral stem-cell support using two different conditioning regimens: in 147 cases STAMP-V regimen and, in 19 patients STAMP-I. The median number of MNC infused was 5.6 x 10^8/kg and a median of 2.06 x 10^6/kg CD 34+ cells. Granulocyte colony-stimulating factors were used in all patients. Antibiotic prophylaxis consisted of Piperacillin/Tazobactam+Amikacin in 63 (40.3%), Ciprofloxacin +Amoxicillin/Clavulanate in 57 (36.5%), 3rd or 4th generation Cephalosporins + Amikacin in 28 (17.9%) and Carbapenem +/- Amikacin in 8 (5.1%).

RESULTS: In a total of 156 of the 166 patients transplanted (94%) the fever appeared in the early period after transplant. The median time for the start of febrile episodes was day +4. Febrile episodes were classified: 1) microbiologically confirmed with bacteriemia in 33 cases (21%), (gram-positive infections in 22 cases (66.6%), and only 11 (33.4%) gram-negative, 2) microbiologically confirmed infections without bacteriemia in 42 cases (26.2%), with a similar proportion of gram-positive and gram-negative agents, 3) clinically documented infections in 46 cases (29.4%), 10 of which were pneumonias, 4) fever of unknown origin in 35 (23%), (66% responded to first-line antimicrobial therapy. In 20 patients empirical systemic antifungal therapy was required. There were 3 treatment-related deaths caused by infections (1.3%). Two of these deaths were caused by gram-negative sepsis, with development of pathologically confirmed respiratory distress syndrome and mucormycosis of the lung and brain. CONCLUSIONS: 1) The majority of the patients treated with high-dose chemotherapy and autologous peripheral stem-cell transplant in our institution developed fever during the first week after transplant. Mortality related to the transplant is very low (1.3%). 2) In our experience, as well as according to the revised bibliography, gram-positive agents account for a high rate of documented bacteriemia.

PCR for detection of fungal pathogens in blood and bronchoalveolar lavage in stem cell transplanted recipients

E. Norberg, L. Klingspor, J. Tollemar, O. Ringden, J. Loeffler (Stockholm, S; Tuebingen, D)

AIM: To present a fungal PCR assay for detection and identification of fungal pathogens in blood and bronchoalveolar lavage (=BAL).

Background: Patients receiving stem cell transplantation (=-SCT) are at high risk to develop deep fungal infections caused by Candida and Aspergillus spp. Deep fungal infections are associated with a high morbidity and mortality in SCT. Early diagnosis and institution of antifungal treatment is crucial. Unfortunately the conventional diagnostic methods of today lack sensitivity or specificity and may be time-consuming.

Material and method: 5 ml of EDTA-blood or BAL was analysed. The method used was the pan-fungal PCR, developed by H. Einsele et al. (J Clin Microbiol 1997 June; 35 (6): 1353-1360) and J. Loeffler et al. (Med. Mycol. 1998 36: 275-279).

Number of patients analysed were six, (2 males and 4 females, ages ranged between 4 months and 40 years). All had received allogeneic stem cell transplantation because of ALL (n=1), CML (n=1), NHL (n=1), AML (n=1), and SCID (n=1), CML (n=1), 1 male and 1 female, age 2 and 13 months respectively. All had clinical suspected fungal infection.

Results: Fungal DNA could be detected in specimens from all 6 patients. Our result was verified by either conventional blood (n=3) or BAL cultures (n=1), ultrasound of liver and spleen and sequencing as a complement of PCR (n=1) or at autopsy (n=1). One patient was positive for C.glabrata in PCR. Blood cultures were negative. Histopathology at autopsy revealed Candida in liver and spleen.

One patient was positive for C.albicans in PCR (we get our samples after first blood culture was positive). Five blood cultures were positive for C.albicans.

One patient was PCR positive for Candida, sequencing was performed as a complement and showed C.krusei. Ultrasound confirmed with typical hepato-splenic Candida lesions. Blood cultures were negative. One patient was positive for C.parapsilosis in PCR (we get our samples after first blood culture was positive). Nine blood cultures were positive for C.parapsilosis.

One patient was positive in BAL for C.albicans in PCR. Culture of BAL confirmed C.albicans.

Conclusion: Fungal PCR performed in blood and BAL for detection and identification of fungal pathogens is a rapid and sensitive method compared to conventional methods and may help to diagnose an invasive fungal infection early.

EBV-infection/disease in allogeneic stem cell transplantation and Cidofovir (CDF) treatment

J. Ullmann, G. Ledderose, G. Jaeger, H.J. Kolb (Munich, D)

Introduction: EBV infection and symptoms presumably related to EBV-disease often occur after allogeneic stem cell transplantation. This study was a retrospective survey among EBV-infection/disease and the efficacy of CDF. 36 CDF applications were evaluated. 5 of 32 CDF-treated pts tested concomitantly positive for CMV, 6 for HHV6 and 1 for VZV reactivation/infection. 1 pt received previous antiviral therapy with Ganciclovir and Foscarnet, 2 pts received Cidofovir combined with Foscarnet and Ganciclovir. 29 pts. received CDF as first line therapy. The dosage of CDF was 1.5 mg/Kg/week. The duration was from 1 application to 7 times. All patients received probenecid and prehydratation. 4 pts suffered from presumed side effects of CDF (vomiting and nausea). CDF treatment had to be stopped in two cases because of creatinine elevation. In 4 pts