11. SAFETY EVALUATION

11.1 ADVERSE EVENTS and SEVERE ADVERSE EVENTS

Immunotherapy and stem cell transplantation were associated with several treatment-related clinical toxic effects. Effects of the stem cell transplantation were similar as for all allogenic stem cell transplantations, especially disorders of hematopoiesis, including anemia and thrombocytopenia, infections, including 3 PJP pneumonias, one fatal HHV-6 infection and two fatal e. coli blood stream infections.

Acute GvHD was experienced by 22,4 % (n=15) of the patients, mostly grade 1/2 acute GvHD of the skin, two patients developed grade 2/3 acute GvHD of the gut.

For Patients with GvHD start of the antibody treatment was delayed in a median of 17 days compared to patients without GvHD.

Induction of late onset acute GvHD (during antibody treatment) was seen in five patients (7,4 %), one patient (1,5 %) developed a steroid sensitive grade 3 GvHD of the GI-tract, one patient (1,5 %) grade 2 GvHD of the GI-tract, both resolved quickly. 3 patients (4,4 %) developed grade 1/2 GvHD of the skin, without the need of systemic (steroid) therapy. No grade 4 GvHD or liver GvHD occurred.

The effects of most interest related to the immunotherapy were fever, pain, tachycardia, hypotension, hypersensitivity reactions and capillary leak syndrome / fluid retention

Fever > 38°C was experienced by nearly all patients, mostly grade 2 or 3, frequent during all cycles, in high fever three patients had generalized seizures.

Pain was observed in all patients and was most frequent during cycle 1, occurring in 96 % (n=65) of patients, and decreasing to 68,4 % (n=46) during cycle 6. The most common sites of pain were the abdomen and the legs.

95,9 % of the courses were administered in the recommended dosage of 20 mg/m^2 of ch14.18/CHO, in most cases lower dosages were given because of severe hypersensitivity reactions. In 11,1 % of the courses a 50 % decrease in the infusion rate of the ch14.18/CHO was given.

	Grade 1/2	Grade 3/4
	Courses (n)	
Hematological toxicity		
Hemoglobin	306 (83,0 %)	53 (14,3 %)
White blood cell	217 (59,0 %)	112 (30,4 %)
Granulocytes (ANC)	182 (49,3 %)	94 (25,5 %)
Platelets	56 (15,2 %)	35 (9,4 %)
Cardinal toxicities		
General condition	296 (80,4 %)	26 (7,1 %)
Skin toxicity	148 (40,1 %)	4 (1,1 %)
Allergy	114 (29,4 %)	52 (13,5 %)
Pulmonary toxicity	59 (15,6 %)	3 (0,8 %)
Gastrointestinal		
Nausea/vomiting	142 (38,7 %)	3 (0,8 %)
Diarrhea	94 (25,5 %)	12 (3,3 %)

Constipation	163 (44,5 %)	0 (0 %)
Stomatitis	32 (8,8 %)	0 (0 %)
Cardiac		
Cardiac function	0 (0 %)	0 (0 %)
QT_c prolongation	2 (1,5 %)	1 (0,8 %)
ECHO: LV/SF	2 (2,0 %)	0 (0 %)
Hypotension	54 (14,7 %)	6 (1,7 %)
Hypertension	7 (1,9 %)	4 (1,1 %)
Renal		
Creatinine	48 (13,2 %)	1 (0,3 %)
Proteinuria	29 (9,1 %)	0 (0 %)
Hematuria	5 (1,6 %)	1 (0,3 %)
Glomerular filtration rate	8 (7,6 %)	0 (0 %)
Tubular phosphate reabsorption	0 (0 %)	1 (25,0 %)
Hemorrhagic Cystitis	0 (0 %)	0 (0 %)
Neurotoxicity		
Central*	20 (5,5 %)	10 (2,7 %)
Peripheral neurotoxicity	9 (2,5 %)	1 (0,3 %)
Liver		
Bilirubin	11 (3,1 %)	8 (2,2 %)
SGOT/SGPT	195 (53,5 %)	43 (11,8 %)
VOD (veno-occlusive disease)[1]	0 (0 %)	0 (0 %)
Pulmonary Toxicity[1]	59 (15,6 %)	3 (0,8 %)
GvHD[2]		
Skin	3 (0,8 %)	0 (0 %)
Gastro-intestinal	1 (0,3 %)	1 (0,3 %)
Liver / CNS	0 (0 %)	0 (0 %)
Adverse Event - no grading		
	Courses n (%)	
Water retention[3]	236 (60,8 %)	
Accommodation disturbances (Pupillotonia)	42 (10,8 %)	
Fever during AB-cycle: received antibiotics	31 (8,0 %)	

[1]Bearman Toxicity (only grades 1 to 3)
[2] NIH Grading
[3] Patient received diuretics - no capillary leak
*One patient developed grade 5 central neurotoxicity and died with signs of brain atrophy/PRES

Table 11-1 Overall Summary of Treatment Emergent Adverse Events

Severe Adverse Events	**Total n (%) number of patients**	**Life threatening /disabling/ fatal n (%)**
Anaphylactic reaction	3 (4,4 %)	1 (1,5 %)
Capillary-leak Syndrome / SIRS	7 (10,3 %)	5 (7,4 %)
Hemolytic anemia	7 (10,3 %)	3 (4,4 %)
Thrombosis Eye	3 (4,4 %) 2 (2,9 %)	 1 (1,5 %)
Infections associated with pathogens		
Fever of unknown origin	22 (32,4 %)	2 (2,9 %)
Bacterial Sepsis: E. coli	3 (4,4 %)	2 (2,9 %)[†]
Salmonella infection	1 (1,5 %)	-
Viral infections		
ADV associated enteritis	7 (10,3 %)	-
BKV infection	1 (1,5 %)	-
CMV	5 (7,4 %)	-
HHV6	2 (2,9 %)	1 (1,5 %)[††]
Influenza	2 (2,9 %)	-
Rota associated enteritis	1 (1,5 %)	1 (1,5 %)
RSV	2 (2,9 %)	-
VZV	1 (1,5 %)	-
PJP pneumonia	3 (4,4 %)	1 (1,5 %)

[†] two patients died of E. coli blood stream infection
[††] one patient died of HHV6-associated encephalitis & pneumonitis