Hemophagocytic lymphohistiocytosis as severe adverse event of antineoplastic treatment in children

Herwig Lackner, Christian Urban, Petra Sovinz, Martin Benesch, Andrea Moser, and Wolfgang Schwinger

Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) during childhood cancer treatment is a rare adverse event posing major diagnostic and therapeutic challenges. Between 1995 and 2006, 6 children developed HLH while on conventional chemotherapy (n=4) or after allogeneic stem cell transplantation (n=2). Treatment of HLH included dexamethasone and etoposide, 2 children additionally received infliximab or daclizumab. Three children survived, whereas 3 children died 2, 5, and 47 days after diagnosis of HLH. HLH is a severe adverse event of childhood cancer therapy. Early diagnosis and immediate initiation of adequate treatment are mandatory to overcome this severe condition.

Key words: hemophagocytic lymhohistiocytosis, children, malignancy.

Citation: Lackner H, Urban C, Sovinz P, Benesch M, Moser A and Schwinger W. Hemophagocytic lymphohistiocytosis as severe adverse event of antineoplastic treatment in children. Haematologica 2008 Feb; 93(2):291-294. DOI: 10.3324/haematol.11704

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon clinical entity characterized by fever, pancytopenia, hepatosplenomegaly and hemophagocytosis in bone marrow, liver or lymph nodes.[1] There are two distinct forms of HLH classified as primary and secondary HLH respectively. The primary, autosomal recessive form, also termed familial hemophagocytic lymphohistiocytosis (FHL), usually occurs in the first years of life and is fatal when untreated. Secondary HLH is associated with a variety of underlying diseases including infections, malignancies and autoimmune diseases.[2,3] The precise pathophysiology of HLH must still be clarified. A major factor causing the manifestations of HLH might be an acquired dysregulation of T lymphocytes and natural killer cells resulting in excessive activation of hemophagocytic monocytes.[1,2,4] Recently, the HLH Study Group of the Histiocyte Society proposed diagnostic guidelines for HLH including fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, low/absent NK-cell activity, hyperferritinemia, and high soluble interleukin 2 receptor (s-IL2-receptor).[3] The clinical course of HLH is usually severe and life-threatening and immediate initiation of therapy is mandatory. Treatment aims to suppress the severe hyperinflammation by chemoimmunotherapy including corticosteroids, cyclosporine A and/or etoposide.[2,3,5] In patients with FHL and in patients with secondary HLH not responding to chemoimmunotherapy, stem cell transplantation (SCT) is a potentially curative treatment option.[6,7]

Malignancy associated HLH (MAHS) usually occurs at initial presentation of malignancy, mainly in patients with leukemia or lymphoma, sometimes even masking the malignancy itself.[2,8-10] In contrast to MAHS, HLH may occasionally develop later during cancer treatment as a consequence of treatment-related immunosuppression. Data describing this distinct condition are extremely rare and treatment recommendations for these children are urgently needed.[2] We report on the clinical course of 6 children with various malignancies who developed HLH during antineoplastic treatment.

Design and Methods

Between 1995 and 2006, 508 consecutive children with various newly diagnosed malignancies were treated at the Division of Pediatric Hematology/Oncology of the Medical University of Graz. Among these, 6 patients (4 females and 2 males aged between 0.5 and 12.5 years) were diagnosed with HLH according to the criteria of the Histiocyte Society.[3] Family history of HLH was negative in all patients. A written informed consent was obtained from patients or their legal guardians. Treatment was performed according to the international treatment protocols approved by the Ethics committee. In addition, this specific

HL and CU equally contributed to the work. Manuscript received May 9, 2007. Manuscript accepted November 14, 2007.
Correspondence: Herwig Lackner, M.D., Division of Pediatric Hematology/Oncology Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Auenbruggerplatz 30, A-8036 Graz, Austria. E-mail: herwig.lackner@meduni-graz.at

study on *HLH as severe adverse event complicating antineoplastic treatment* was approved by the local Ethics committee. Patient characteristics and oncologic pre-treatment are summarized in Table 1. Diagnoses included acute lymphoblastic leukemia (ALL) (n=2), acute myelogenous leukemia (AML) (n=2), recurrent medulloblastoma (n=1) and Ewing sarcoma (n=1). Four of the 6 patients were diagnosed with HLH during conventional hemato-oncologic treatment, whereas 2 patients developed HLH on day 57 and 24 after allogeneic stem cell transplantation (SCT). Stem cell donors were a matched unrelated donor (MUD) in patient 5 and the HLA identical mother in patient 6. Both received reduced intensity conditioning (RIC) including fludarabine and melphalan, followed by immunosuppressive treatment with prednisone and cyclosporine A. In addition, patient 5 received mycophenolate mofetil. At onset of HLH, all 6 patients underwent supportive care with granulocyte colony stimulating factor (G-CSF), broad spectrum antibiotics and antimycotics, blood transfusions and parenteral nutrition via central venous lines.

Results and Discussion

Diagnosis of HLH

All children initially presented with prolonged pancytopenia, hepatosplenomegaly and fever refractory to antimicrobial therapy. Three patients had CNS-symptoms including seizures, headache and encephalopathy with impaired vision/swallowing. Analysis of CSF showed pleocytosis and elevated protein, whereas MRI was normal in these patients. Different infectious agents were identified by PCR or antigen detection as presumed triggers of HLH including influenza A virus, Epstein Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV6) and adenovirus. Two patients (patients 2 and 5) also presented infection with aspergillus fumigatus. Since there was no response to common supportive treatment, serum parameters providing the diagnosis of HLH were evaluated in 5 out of the 6 patients showing marked elevations of ferritin, s-IL2-receptor and triglycerides (Patient 1 had a fulminant clinical course and diagnosis of HLH was established only by bone marrow cytology 2 days before the patient died). Definitive diagnosis of HLH was made by bone marrow aspiration in all patients showing increased numbers of histiocytes, phagocytosing red cells, platelets and white cells. At onset of HLH, renal function was normal in all patients, whereas liver function was impaired in 5 patients with elevated serum bilirubin levels ranging between 1.49 and 4.1 mg/dL. Special studies including NK cell function and intracellular perforin were not carried out in our patients. However, all patients fulfilled at least 5 out of 8 clinical criteria of the Histiocyte Society for diagnosis of HLH (Table 2).

Treatment of HLH and outcome

All patients underwent treatment of the presumed triggering infectious agents with immunoglobulines and specific antiviral drugs, e.g. amantadine (80 mg/kg/d for 5 days) for influenza A virus, gancyclovir (10 mg/kg/d for 10

Table 1. Hemophagocytic lymphohistiocytosis: patient characteristics and pre-treatment.

Patient	*Sex*	*Age at diagnosis of malignancy*	*Oncologic diagnosis (years)*	*Oncologic pre-treatment (protocol)*	*Oncologic status at onset of HLH*	*Absolute lymphocytes/μL*	*Interval from diagnosis to HLH (months)*
1	M	0.5	ALL relapse	ALL-BFM 90 relapse→ ALL-REZ BFM 90	maintenance therapy (TG/MTX) since 8 months	0	42
2	F	16	AML FAB M2	AML-BFM 93	maintenance therapy (TG/ARA-C) since 11.5 months	220	17
3	M	1	Recurrent medulloblastoma	surgery, chemotherapy (HIT-SKK 92) relapse→ γknife chemotherapy (IFO/VP-16)	prolonged pancytopenia after chemotherapy (IFO/VP-16)	455	7
4	F	12.5	Ewing sarcoma	Euro-EWING 99	prolonged pancytopenia after 6 courses of chemotherapy	51	4
5	F	7.5	ALL relapse	ALL-BFM 95 1. relapse→ALL-REZ BFM 96 2. relapse→ALL-REZ BFM Pilot 02 →3. remission + aspergilloma RIC + MUD – BMT (Flu/Mel/alemtuzumab)	day +57 after BMT immunosuppression (PRED, MMF, CyA)	1.050	49
6	F	9.5	AML FAB M2	AML-BFM 2004 →irreversible aplasia (HHV_6) →RIC + allo-BMT (mother) (Flu/Mel/ATG)	day +24 after BMT immunosuppression (PRED, CyA)	65	3

HLH: hemophagocytic lymphohistiocytosis; ALL: acute lymphoblastic leukemia; ATG: antithymocyte globulin; HHV6: human herpesvirus 6; AML: acute myelogenous leukemia; IFO: ifosfamide; ARA-C: cytarabine; RIC: reduced intensity conditioning; VP-16: etoposide; BMT: bone marrow transplantation; MUD: matched unrelated donor; PRED: prednisone; TG: thioguanine; Flu: fludarabine; MMF: mycophenolate mofetil; MTX: methotrexate; Mel: melphalan; CyA: cyclosporine A.

days) for CMV, HHV6 or EBV, ribavirine (33 mg/kg starting dose, then 4×16 mg/kg on day 2-5 followed by 3×8 mg/kg on day 6-14) for adenovirus, and liposomal amphotericin B (5 mg/kg/d) for aspergillus. Patient 1 received no specific anti-HLH therapy, since diagnosis of HLH was made only 2 days before death. Patient 2 and 3 received dexamethasone (DXM) (10 mg/m^2/d for 35 days and 5 days) in combination with etoposide (150 mg/m^2/dose once weekly) 2 and 3 times respectively. Despite this treatment, both patients died 47 days and 5 days after diagnosis of HLH. Patient 4 received DXM (10 mg/m^2/d for 30 days) and 2 doses of infliximab (5 mg/kg/dose with an interval of 3 weeks), a monoclonal antibody against tumor necrosis factor-α (TNF-α). Her clinical symptoms improved within 10 days, and she is now, 1 year after occurrence of HLH clinically well without evidence of HLH or recurrent malignancy. Patient 5 developed HLH in combination with CNS symptoms 57 days after MUD-BMT for recurrent ALL. The patient underwent ventilation support for 18 days. Her HLH-specific treatment included DXM (10 mg/m^2/d for 45 days), 5 doses of etoposide (150 mg/m^2/dose in weekly intervals) and 5 doses of daclizumab (1 mg/kg/dose in weekly intervals), a monoclonal anti-CD25 antibody. The patient completely recovered from HLH within 2 weeks but died of chronic graft versus host disease 11 months later. Patient 6 developed HLH with CNS symptoms 24 days after allo-SCT for refractory AML. She improved after prolonged treatment with DXM (10 mg/m^2/d for 70 days), and is now, 2 years after BMT, clinically well without evidence of HLH or recurrent malignancy. Since 1969, some sporadic cases had been published describing an hemophagocytic syndrome as a rapidly progressive and fatal disease terminating the clinical course of patients with ALL or lymphoma (mainly T-cell type). This syndrome was variously called histiocytic medullary reticulosis (HMR), HMR-like syndrome, malignant histiocytosis and reactive hemophagocytic syndrome.[11-13] Since 1991, the term HLH is generally accepted to describe this condition.[3] The occurrence of HLH during antineoplastic treatment is still a very rare and usually fatal event. The registry of the BFM-ALL trials from 1981-2001 holds data on 4 out of 971 T-ALL patients who developed HLH and none of them survived.[14]

In agreement with these data, only 1 out of 4 patients with HLH during conventional antineoplastic treatment survived this serious complication in our study. Interestingly, 2 of our patients had HLH as a complication of oncologic treatment for solid tumors. The occurrence of HLH in the setting of therapy for solid tumors has never been reported before, since so far HLH has only been seen in patients with leukemia or lymphoma. There are some case reports describing HLH as a complication after SCT.[15-17] Fludarabine based conditioning regimens are suspected to be additional non-specific triggers for HLH after SCT.[17] Interestingly, both of our 2 patients with HLH following SCT underwent RIC including fludarabine.

There are several problems and questions regarding the optimum management of children with HLH during antineoplastic treatment. Early diagnosis might be frequently

Table 2. Hemophagocytic lymphohistiocytosis: symptoms, diagnosis, therapy.

Patient	*Fever*	*Prolonged pancytopenia*	*Hepatosplenomegaly*	*CNS*	*Triggering infection*	*Hemophagocytosis in bone marrow*	*HLH-serum parameters (maximum values)* *Ferritin ng/mL*	*s-IL-2-receptor*	*Triglycerides ng/mL*	*Fibrinogen mg/mL*	*Therapy*	*Outcome*
1	+	+	+	+ seizures	influenza A	+	n.t.	n.t.	n.t	n.t.	Ig, amantadine	died 2 d after diagnosis of HLH
2	+	+	+	–	EBV aspergillus	+	81.280	21.840	287	118	Ig, gancyclovir DXM (35d) VP-16 3 x	died 47 d after diagnosis of HLH
3	+	+	+	–	CMV	+	9.144	>2.940	88	285	Ig, gancyclovir DXM (5d) VP-16 2 x	died 5 d after diagnosis of HLH
4	+	+	+	–	HHV6	+	3.650	10.000	335	184	Ig DXM (30d) Infliximab 2 x	survived
5	+	+	+	+ encephalopathy (impaired vision and swallowing) seizures	EBV HHV6 CMV aspergillus	+	12.700	8.300	638	370	Ig, gancyclovir, foscavir ventilation support (18d), DXM (45 d) VP-16 2 x daclizumab 5 x	survived, but died due to chronic GVHD 1 year after BMT
6	+	+	+	+ headache fatigue	adenovirus	+	6.000	20.000	254	148	Ig, ribavirine DXM (70 d)	survived

HLH: hemophagocytic lymphohistiocytosis; Ig: immunoglobulines; EBV: Epstein-Barr virus; CNS: central nervous system; DXM: dexamethasone; n.t.: not tested; GVHD: graft-versus-host disease; CMV: cytomegalovirus; VP-16: etoposide; HHV6: human herpesvirus 6; s-IL-2-receptor soluble interleukin 2 receptor.

delayed since the condition might be misinterpreted as chemotherapy induced myelodepression with sepsis. In children with HLH after SCT, differential diagnoses include a variety of other systemic inflammatory syndromes such as engraftment syndrome, disseminated intravascular coagulation and capillary leak syndrome. Should patients with HLH during antineoplastic treatment be treated according to the same treatment protocols as patients with other forms of HLH. Many investigators might be reluctant to immediately initiate HLH-specific treatment including DXM, etoposide and cyclosporine A in these heavily pre-treated patients. The use of the new so called biologicals in the treatment of HLH has not yet been introduced into the current treatment protocols. There are single case reports describing the successful use of daclizumab, a monoclonal anti-CD25 antibody against s-IL2-receptor as well as infliximab, a monoclonal anti-TNF-α antibody in patients with HLH.[18,19] Supported by these case reports, 2 of our patients were successfully treated with daclizumab and infliximab respectively. Some investigators suggest that cytokines (e.g. G-CSF), as well as prolonged intravenous nutrition including soluble lipids, might provide a continuous stimulation of the monocyte/macrophage system resulting in HLH.[3,20] It remains, therefore, debatable whether G-CSF and/or parenteral nutrition containing soluble fats should be given in patients with HLH.

In conclusion, HLH as a complication of antineoplastic treatment is still a rare and life-threatening serious adverse event. Early diagnosis by analysis of serum parameters and detection of hemophagocytosis in bone marrow is absolutely mandatory in order to immediately initiate adequate and aggressive treatment. The role of the new biologicals, including the monoclonal antibodies daclizumab and infliximab, remains to be defined. Further clinical data describing the clinical course and the management of children with HLH during antineoplastic treatment are urgently awaited.

Authorship and Disclosures

HL co-designed the study, enrolled patients, analyzed results and wrote the manuscript; CU co-designed the study,enrolled patients,contributed to data registration and quality control; PS enrolled patients,contributed to data registration and quality control; MB contributed to data registration and quality control, and provided comments on the manuscript; AM enrolled patients,contributed to data registration and quality control; WS enrolled patients,contributed to data registration and quality control. The authors reported no potential conflicts of interest.

References

1. Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis 2000;6:601-8.
2. Janka GE, Schneider EM. Modern management of children with haemophagocytic lymphohistiocytosis. Br J Haematol 2004;124:4-14.
3. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
4. Schneider EM, Lorenz I, Walther P, Janka-Schaub GE. Natural killer deficiency: a minor or major factor in the manifestation of hemophagocytic lymphohistiocytosis? J Pediatr Hematol Oncol 2003;25:680-3.
5. Imashuku S. Advances in the management of hemophagocytic lymphohistiocytosis. Int J Hematol 2000;72: 1-11.
6. Horne A, Janka G, Maarten Egeler R, Gadner H, Imashuku S, Ladisch S, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol 2005;129:622-30.
7. Ouachee-Chardin M, Elie C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics 2006;117:e743-50.
8. O'Brien MM, Lee-Kim Y, George TI, McClain KL, Twist CJ, Jeng M. Precursor B-cell acute lymphoblastic leukemia presenting with hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2006;19(Epub ahead of print).
9. Blatt J, Weston B, Belhorn T, Hamrick H, Maia D. Childhood non-Hodgkin lymphoma presenting as hemophagocytic syndrome. Pediatr Hematol Oncol 2002;19:45-9.
10. Urban C, Lackner H, Schwinger W, Beham-Schmid C. Fatal hemophagocytic syndrome as initial manifestation of a mediastinal germ cell tumor. Med Pediatr Oncol 2003;40: 247-9.
11. Clark BS, Dawson PJ. Histiocytic medullary reticulosis presenting with a leukemic blood picture. Am J Med 1969;47:314-7.
12. Haubenstock A, Base W, Bettelheim P, Hinterberger W, Pavelka M, Thaler E, et al. Malignant histiocytosis with unusual features. Cancer 1984;53: 1574-8.
13. Liang DC, Chu ML, Shih CC. Reactive histiocytosis in acute lymphoblastic leukemia and non-Hodgkin's lymphoma. Cancer 1986; 58:1289-94.
14. Trebo MM, Attarbaschi A, Mann G, Minkow M, Kornmuller R, Gadner H. Histiocytosis following T-acute lymphoblastic leukaemia: a BFM study. Leuk Lymphoma 2005;46: 1735-41.
15. Choi AY, Matsushima HK, Nishimura J, Inaba S, Nawata H, Muta K. Hemophagocytic syndrome: a rare complication of allogeneic non-myeloablative hematopoietic stem cell transplantation. Bone Marrow Transplant 2002;29:799-801.
16. Sreedharan A, Bowyer S, Wallace CA, Robertson MJ, Schmidt K, Woolfrey AE, et al. Macrophage activation syndrome and other systemic inflammatory conditions after BMT. Bone Marrow Transplant 2006; 37:629-34.
17. Ferreira RA, Vastert SJ, Abinun M, Foster HE, Modesto C, Olive T, et al. Hemophagocytosis during fludarabine-based SCT for systemic juvenile idiopathic arthritis. Bone Marrow Transplant 2006;38:249-51.
18. Tomaske M, Amon O, Bosk A, Handgretinger R, Schneider EM, Niethammer D. α-CD25 antibody treatment in a child with hemophagocytic lymphohistiocytosis. Med Pediatr Oncol 2002;38:141-2.
19. Henzan T, Nagafuji K, Tsukamoto H, Miyamoto T, Gondo H, Imashuku S, et al. Success with infliximab in treating refractory hemophagocytic lymphohistiocytosis. Am J Hematol 2006; 81:59-61.
20. Glasser L, Legolvan M, Horwitz HM. Florid histiocytic hemophagocytosis following therapy with long acting G-CSF (pegfilgastim). Am J Hematol 2007;82:753-7.