Karolinska Institutet

Institutionen för kvinnor och barns hälsa

CLINICAL STUDIES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

AKADEMISK AVHANDLING
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ABSTRACT

Background and aims: The term hemophagocytic lymphohistiocytosis (HLH) comprises two main disease entities: the primary, familial form (FHL) and an acquired, secondary form (sHLH). FHL is autosomal recessive in inheritance, typically affects very young children and is almost invariably fatal unless treated. Secondary HLH typically occurs in older children and adults. However, sHLH may also affect infants and FHL may affect adults. In the absence of reliable functional cell studies, a genetic diagnosis or a family history of HLH, differentiation between the two at onset is virtually impossible. Other inherited syndromes in which HLH can develop are X-linked lymphoproliferative disease (XLP), Chédiak-Higashi syndrome (CHS), and Griscelli syndrome type II (GS2). HLH signs and symptoms are related to hyperinflammation after a triggering infection, and include persisting fever, hepatosplenomegaly and non-malignant infiltration in many organs, including bone marrow, liver, spleen and central nervous system (CNS) of activated T lymphocytes and macrophages, the latter involved in hemophagocytosis. Neurological symptoms can be present already at onset. Laboratory investigations typically reveal cytopenia, elevated values of liver enzymes, ferritin, cytokines and triglycerides, and a coagulopathy. In FHL, natural killer cells are normal in number but show reduced or absent function.

The aims of this thesis include description of disease characteristics at onset as well as presentation of treatment results prior to and after hematopoietic stem cell transplant (HSCT) in children with HLH **(*Paper I*)**, and in the other inherited HLH-related diseases **(Paper III)**. Furthermore, the aims include description of the frequency and character of acute CNS disease and of CNS sequelae (**Paper II**), and to evaluate risk factors for adverse outcome **(Papers II, IV** and **V)**.

Methods: The studies were conducted on data from patients recruited from the databases of the international treatment study protocols HLH-94 (**paper I**, n=249; **paper II**, n=193) and HLH-2004 (**paper V**, n=297). In **paper III** patients were recruited from both protocols. In **paper IV,** the data were collected as part of a European collaborative effort.

Results: At a median follow-up of 6 years, overall 5-year probability of survival in the HLH-94 treatment study was 55%, and 5-year survival post-transplant was 67%. Altogether, 73% of the patients received transplants or achieved long-term remission without HSCT. There was no significant difference in survival for patients with familial disease. Patients with a presumed secondary disease were older, more often female, and less frequently had CNS disease at onset **(paper I)**. CNS disease at onset was common, (63%) and an important risk factor for both death and neurological late effects. Neurological sequelae were present in 15% upon follow-up **(paper II)**. Seven of nine patients with GS2, XLP or CHS could receive transplants after HLH therapy, and one had long-term remission without HSCT. At last follow-up (mean 6 years), eight of nine were alive **(paper III)**. Risk factors for early pre-transplant death that remained significant in both **papers IV** and **V** were hyperbilirubinemia at onset and hyperferritinemia and thrombocytopenia after two weeks.

Conclusion: In conclusion, survival has increased dramatically in patients with HLH with the introduction of the HLH-94 treatment protocol, but a large proportion of patients still succumb to the disease. Novel treatment strategies need to be developed in order to reduce early pre-transplant mortality, but also to reduce transplant-related mortality and morbidity. CNS-HLH is frequent, and a risk-factor for adverse outcome. Thorough evaluation of acute CNS symptoms and signs, as well as close neurological follow-up is important. Patients with HLH-associated syndromes may also benefit from HLH-94 treatment. There are simple laboratory parameters that may help in risk estimation of HLH patients, and these - alone or taken together - may be used to adapt treatment intensity.

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