Co-existence of thrombocytopenia and hyperleukocytosis (‘critical period’) as a risk factor of haemorrhage into the central nervous system in patients with acute leukaemias

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Abstract—The aim of this work was to examine whether the risk of death i.a. due to haemorrhage into the central nervous system (CNS) is higher during some phases of acute myeloblastic leukaemia (AML), lymphoblastic leukaemia (ALL), and the blastic phase of chronic myelogenous leukaemia (BP) when two important risk factors that worsen the prognosis are simultaneously present: low thrombocytopenia and hyperleukocytosis. Clinical and post-mortem neuropathological examination was performed in 143 patients, aged 17–76 years, who died from AML (80 cases), BP (38), and ALL (25). Periods with co-existence of thrombocytopenia below $25 \times 10^9$ per l and hyperleukocytosis above $100 \times 10^9$ per l were identified after plotting the results and were termed the ‘critical period’ (CP). The study showed that the risk of death was disproportionately high during the CP. This finding was obtained in all patient groups, although it involved mainly patients with AML and BP, i.e. leukaemias with the highest frequency of hyperleukocytosis in peripheral blood. It is suggested that the risk of death during the CP is so high because leukaemic cells are a potent synergistic factor to thrombocytopenia in causing CNS haemorrhage. When a CP is detected, hyperleukocytosis and thrombocytopenia should be controlled and treated aggressively: leukapheresis and platelet concentrates should be administered. Patients with CP should not be given packed red blood cells, in order to avoid a further increase in blood viscosity, which is already high due to hyperleukocytosis. In fact, anaemia during the CP should be regarded as a potentially life-saving factor.

Key words: Leukaemia; thrombocytopenia; hyperleukocytosis; CNS haemorrhage.

1. INTRODUCTION

Haemorrhage into the central nervous system (CNS) in patients with leukaemia is usually fatal because it is difficult to control and is frequently very extensive [1, 2].

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The risk of haemorrhage is particularly high when the platelet count falls below $25 \times 10^9$ per l. One underlying cause is thrombocytopenia, resulting from infiltration of the bone marrow by leukaemic cells, but other conditions, such as disseminated intravascular coagulation, shock, infection, chemotherapy, and bone marrow transplantation, may also play an important role in the haemorrhagic event [3–7].

Although leukaemic and lymphomatous cells are considered to be responsible for CNS infiltrates rather than as factors facilitating CNS haemorrhage, they should also be taken into account as a risk for bleeding into the CNS [8–10]. Leukostasis, particularly within the capillary network, may be of some importance in disruption of the vascular wall [11–13] and in the development of brain oedema [14]. This can explain why the frequency of haemorrhage is highest among patients with myelomonoblastic and acute monoblastic leukaemias, when the aggressiveness of the leukaemic cells against the vessels is notable. Massive intracerebral leukaemic infiltrates are accompanied by local ischaemia and capillary stasis, which are factors promoting haemorrhage [12, 15]. The release of lysokinase from leukaemic cells may directly activate fibrinolysis and intravascular coagulation [16]. In previous reports and in everyday practice, the two mentioned risk factors of leukaemia are examined separately from each other.

The aim of this work was to examine whether the risk of death i.a. due to haemorrhage into the CNS is significantly higher during some phases of acute myeloblastic leukaemia (AML), lymphoblastic leukaemia (ALL), and the blastic phase of chronic myelogenous leukaemia (BP) when two important risk factors of CNS involvement that worsen the prognosis are simultaneously present: low thrombocytopenia and hyperleukocytosis. The clinical significance of a better understanding of this problem might be expressed in prevention or treatment procedures in this dangerous constellation of risk factors.

2. MATERIALS AND METHODS

Clinical and post-mortem neuropathological examination was performed in 143 patients of both sexes, aged 17–76 years (mean 42.6 years), who consecutively died from AML (80 cases), BP (38), and ALL (25). Patients with confirmed disseminated intravascular coagulation were not taken into consideration in the study. AML patients received chemotherapy according to the TAD regimen. ALL patients were treated according to the Hoelzer protocol. Supportive therapy included transfusions of packed red blood cells, platelet concentrates, and blood preparations, and was administered according to generally accepted principles. Platelet and white cell counts in peripheral blood were repeatedly obtained from each patient. $25 \times 10^9$ per l was accepted as the critical level of thrombocytopenia and of high risk of haemorrhage into the CNS. On the basis of our previous studies and values given in the literature [11, 12], we took $100 \times 10^9$ per l as the level of leukocytosis critical for leukostasis and perivascular infiltrates in the brain and