Bleeding and thrombosis in childhood cancer

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Defects of hemostasis in patients with cancer have been first described by Trousseau in 1865,[1] and Morrison studied altered coagulation in patients with malignancy as early as 1932.[2] The first described abnormality of hemostasis in malignancy was that of hypercoagulability and thrombosis and the first large survey of blood changes in cancer patients showed accelerated bleeding times in over 60% of patients studied. This presentation discusses thrombotic and hemorrhagic disorders that occur in children with solid tumors and hematological malignancies.

Thrombosis in children with solid tumors

Besides thrombosis occurring in children with hematological malignancies symptomatic vascular accidents are also reported in children with solid tumors, e.g. Ewing's sarcoma, malignant brain tumor, nephroblastoma, neuroblastoma, rhabdomyosarcoma, and osteosarcoma respectively.[3-6]

Thrombosis in children with hematological malignancies

Symptomatic thromboses in pediatric hematological malignancies have not only been reported in acute lymphoblastic leukemia (ALL) but also in children with Hodgkin's disease, histiocytosis, and paroxysmal nocturnal hemoglobinuria.

The majority of symptomatic vascular accidents with and without venous central lines,[7] however, occurred in children with ALL. Alterations in hemostasis frequently observed in patients with ALL are well documented in children receiving L-asparaginase (ASP) as a single agent or in combination with vincristine or prednisone or dexamethasone, sometimes complemented by an anthracycline. E. coli ASP preparations of different sources and dosages and Erwinia ASP are involved in hemostatic alterations and venous occlusion. Depending on the treatment protocol used the rate of symptomatic thrombosis varied between 0 and approximately 11%.[8-11]

Differences in the pharmacokinetics and pharmacodynamics of various asparaginase preparations (Erwinia asparaginase, E. coli asparaginase, PEG asparaginase) have been reported in the literature. Results of a dose reduction study reported in 1996 show a dose-dependent down-regulation of coagulation and fibrinolytic proteins with improvement in children treated with 2500 IU/m^2 Kyowa ASP compared to 5000 IU/m^2 and 10.000/m^2 Kyowa ASP. Changes were less pronounced in 2500 IU/m^2 and were similar to those changes documented in children treated with 10.000 IU/m^2 Bayer E. coli ASP. Whereas complete asparagine depletion was achieved in all children studied, increased asparaginase activity clearly correlated with the decrease of coagulation and fibrinolytic proteins.[7]

We recently have shown that the distribution or prothrombotic risk factors in ALL patients are no different from population-based healthy controls. However, depending on the treatment protocol used, different incidences of severe thrombotic events have been reported with up to 47% associated with prothrombotic risk factors.[9]

Until today, however, no evidenced-based sufficiently powered treatment studies with respect to primary thrombosis prevention in children with hematological malignancies are available.[12-14] The results of the PROTEKT trial, an open-label randomized controlled trial of LMWH for the prevention of central venous line-related thrombosis did not show a clear efficacy for children treated with the LMWH reviparin-natrium compared with the house standard. In addition, in the PAARKA trial Mitchell *et al.* randomized children with ALL to either antithrombin substitution or no antithrombin administration. In the latter study, which was not powered to answer the question of efficacy and safety a trend towards a protective effect against thrombosis was observed in the antithrombin treatment arm.

Bleeding associated in children with solid tumors

The most common hemostatic defect in cancer children is thrombocytopenia, which usually develops late in the course of the illness. Less frequently, chronic disseminated intravascular coagulation (DIC), liver failure secondary to metastases or the synthesis of dysfunctional clotting-factor molecules are seen.[15]

Thrombocytopenia is most often the result of suppression of marrow platelet production by malignancy, chemotherapy, or radiation treatments. In addition, rarely children with malignancy develop microangiopathy (HUS or TTP) accompanied with renal failure, anemia and thrombocytopenia. This occurs most commonly when cisplatin, bleomycin or cyclosporine A have been administered.

In adults many tumors can activate coagulation and fibrinolysis in an effort to facilitate the implantation of metastatic cells. The release of cells from the primary tumor can be augmented by the action of proteolytic or fibrinolytic enzymes on nearby blood vessels, and the growth and proliferation of disseminated tumor cells may be facilitated by the formation of a local fibrin meshwork. Laboratory evidence of activation of coagulation in the early and late stages of solid tumors is also seen in children. However, hemorrhage as a result of DIC which does not occur unless clotting factor depletion is severe (fibrinogen <100 mg/dL, factor VIII <30%, platelet count <50.000/uL) is most often found in children with disseminated neuroblastoma and rarely occurs with other tumors.

Bleeding in children with hematologic malignancies

In children with lymphoproliferative disorders causes of hemorrhage are diverse, although thrombocytopenia induced by bone marrow disease or chemotherapy is the most common problem.

DIC can complicate acute lymphoblastic leukemia (ALL) as well as acute promyelocytic (APL) or monocytic leukemia, and approximately 5-10% of children and adults have laboratory evidence of DIC. Even higher rates of DIC have been reported to occur after chemotherapy is initiated. In children some of these abnormalities have been reported secondary to l-asparaginase administration.[16] Following ASP administration also bleeding episodes have been reported mainly as *hemorrhagic transformations* of a cerebral venous thrombosis.

The coagulopathy in patients with myeloid leukemia, particular APL is often complex and consists of classic DIC, systemic fibrinolysis, or hemostatic and vascular defects produced by proteolytic enzymes.[17] As in adults, children with AML and FAB type 3 morphology who were initially treated with ATRA showed an earlier normalization of coagulation abnormalities compared with non-treated children.[18,19]

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