Hyperfibrinolysis and acquired factor XIII deficiency in newly diagnosed pediatric malignancies

Bleeding events in patients with leukemia or malignant tumors can seriously complicate diagnostic interventions or therapeutic procedures, and may increase cancer-associated morbidity and mortality. Bleeding signs due to thrombocytopenia are frequent, especially in patients with malignant hematologic diseases. However, some cancer patients show a significant impairment of the plasmatic coagulation system, resulting in abnormal laboratory clotting tests or even in clinically apparent bleeding events.

Acute myeloid leukemia (AML), especially subtype M3 according to the French-American-British (FAB) classification, is frequently associated with hemorrhage due to hyperfibrinolysis and disseminated intravascular coagulation (DIC). Paraneoplastic coagulopathy occurs in approximately 14% of AML and this clearly contributes to early mortality. Only limited data on acquired factor XIII deficiency and DIC in cancer patients are available so far.[1-3] Up to now, the incidence of coagulation disorders and the affected clotting factors in cancer patients have not been systematically assessed, especially in pediatric patients.

Guidelines do not consistently recommend screening of coagulation parameters in cancer patients at time of diagnosis. Prothrombin time (PT), activated prothrombin time (aPTT) and fibrinogen tests are available in most laboratories and might, therefore, be done regularly. However, factor XIII deficiency, commonly present in hyperfibrinolysis and typically observed in DIC, is not detected by these tests. Factor XIII is a transglutaminase that cross-links fibrin chains and is, therefore, essential for the final step of hemostasis. Whereas factor XIII levels of approximately 3-10% are sufficient to prevent spontaneous bleeding, levels above 30-50% are necessary for surgical intervention.[4] D-dimers (degradation products from cross-linked fibrin) are known to be sensitive for activated coagulation pathways. Unlike elevated D-dimers, acquired factor XIII deficiency in an activated clotting system can cause severe and fatal bleeding.[4] Although publications about factor XIII in cancer date back to the 1970s, and although factor XIII can be easily and safely substituted, only a few reports have been published on this issue.[1-3] We report a series of 9 children with malignant diseases that were associated with hyperfibrinolysis and factor XIII deficiency at time of diagnosis. A summary of patient data is provided in Table 1. Three patients showed the well-known problem of coagulopathy in AML (Patients 1-3). The other patients suffered from

Table 1. Patients' data with diagnoses, bleeding signs, need for transfusions, coagulation test values and general outcome.

Patient	Age/ Gender	Diagnosis	Bleeding signs at presentation	Prophylactic transfusions	Peri-interventional bleeding	Therapeutic transfusions	Post-interventional bleeding	PT[1] (%)	aPTT[2] (s)	Fibrinogen[1] (g/L)	Factor XIII[1] (%)	D-dimers[2] (mg/L)	Factor XIII recovery	General outcome
Acute myeloid leukemia (AML)														
1	15 / f	AML FAB M5	No	No	No, interventions postponed to recovery	No	No	33	58	0.7	14	19.3	After induction therapy	DOD due to relapse after six months
2	16 / f	AML FAB M3	Hematomas	Factor XIII	No	No	No	43	<36	0.6	15	32.2	During induction therapy	CR
3	11 / f	AML FAB M5	Hematomas and hematemesis	FFP, factor XIII	Severe lung bleeding	Factor XIII daily	No	57	37	0.9	<10	>33	No	No remission, DOD after 52 days
Acute lymphoblastic leukemia (ALL)														
4	7 / m	T-ALL, hyperleukocytosis	No	Factor XIII	No	No	No	23	43	0.4	15	23.1	During induction therapy	CR
5	16 / m	T-ALL, hyperleukocytosis	Multiple foci of cerebral infarction (leukapheresis)	Factor XIII	No	No	No	40	44	0.8	23	21.3	During induction therapy	CR
6	17 / m	c-ALL	Skin petechiae	Factor XIII	No	No	No	39	38	0.9	37	n. d.	Day 33	CR
Solid malignant tumors														
7	2 / m	Neuroblastoma stage IV, myc-n amplification	No	Factor XIII daily	Severe gastrointestinal and catheter tunnel bleeding	Red cells, platelets, FFP, factor XIII repetitively	No	60	37	0.7	<10	>33	After first course of chemotherapy	CR
8	3 / m	Non-Hodgkin's lymphoma (Burkitt's lymphoma)	No	No	Severe abdominal bleeding	Red cells, FFP, factor XIII	No	443	513	1.13	293	5.8	During induction therapy	CR
9	7 / f	Disseminated alveolar rhabdomyosarcoma	No	No	Prolonged severe bleeding out of catheter tunnel	Red cells, FFP, fibrinogen, factor XIII	No	50	48	0.6	13	>33	After first course of chemotherapy, decline at time of relapse	DOD due to relapse after six months

f: female; m: male; FFP: fresh frozen plasma; n.d.: not determined; DOD: death of disease; CR: complete remission. Range of normal: PT (70-100%), aPTT (37-40 s), fibrinogen (2.5-4.0 g/L), factor XIII (70-100%), D-dimers (<0.5 mg/l). [1]The minimum of pathological values is indicated. [2]The maximum of pathological values is indicated. [3]Parameters measured after postsurgical bleeding and transfusion.

acute lymphoblastic leukemia (ALL) (Patients 4-6) or solid tumors, such as neuroblastoma (Patient 7), non-Hodgkin's lymphoma (Patient 8) and rhabdomyosarcoma (Patient 9). The patients' clinical presentation varied from no symptoms to severe, life-threatening bleeding events. There was no clear inverse correlation between the clinical severity of the bleeding and the degree of factor XIII deficiency. Except for one case of an AML refractory to chemotherapy, coagulopathy resolved entirely after specific treatment had been initiated. Even in common ALL (c-ALL), the most frequent malignant disease in childhood, we found one case (Patient 6) with mild factor XIII deficiency. Our findings underline the observation that bleeding events in ALL patients at time of diagnosis predominantly occur in T-lineage ALL with large tumor burden and have been identified as an independent risk factor.[1] Although coagulopathy in patients with solid tumors is reported to be rare,[5-7] all 3 patients showed a clinically significant bleeding, and only substitution of factor XIII resolved bleeding signs. Up to now, no case has been published reporting alterations of the clotting system and severe bleeding in neuroblastoma (Patient 7).

Whereas some of our patients with cancer-associated coagulopathy developed severe or life-threatening bleeding, we also identified patients with asymptomatic intravascular activation of the coagulation pathway and factor deficiency. These might be at high risk for bleeding during or after invasive procedures, e.g. lumbar puncture, central venous catheter implantation or tumor biopsy (Patients 7, 8 and 9). We decided to administer factor XIII as primary prophylaxis in cases in which factor XIII levels ranged beneath 40% prior to a planned intervention (Patients 2, 4, 5 and 6), or as secondary prophylaxis after a major or repetitive bleeding without quick factor XIII recovery (Patients 3, 7 and 8).

First-line treatment for cancer-associated coagulopathy including life-threatening hyperfibrinolysis and DIC is the treatment of the malignancy itself.[6,7] Even if there is no measurable tumor response, beneficial effects of cytostatic treatment on the tumor's procoagulant activity have been described.[3] However, chemotherapy may not achieve a response fast enough in critically bleeding patients. Treatment options in urgent cases are: anticoagulants (e.g. heparin) to stop intravascular clotting processes or substitution of platelets, red cells, clotting factors (e.g. fresh frozen plasma (FFP), factor XIII or antithrombin III) or antifibrinolytics to inhibit residual fibrinogenolysis and fibrinolysis.[1,6,8] However, there is no expert consensus regarding baselines and indication for each drug application. In particular, therapy of DIC must be highly individualized. Factor XIII concentrate seems to be efficient in improving hemostasis by a quick and sufficient increase in its plasma factor activity. We did not observe any side effects in our patients. Except for invasive procedures we do not recommend substitution in asymptomatic patients whereas patients with clinical symptoms seem to benefit from targeted substitution of factor XIII rather than from FFP.

Nine patients were selected for this report due to their different underlying malignant entities and their representative clinical courses; several patients with initially asymptomatic and prophylactically-treated factor XIII deficiency are not described. Among approximately 350 pediatric cancer patients (excluding brain tumors) who were treated in our center for pediatric hematology and oncology from 2005 to 2012, the reported patients alone account for an estimated incidence of at least 2% of severe factor XIII deficiency and associated bleeding complications. Since we did not assess factor XIII levels on a routine basis in all patients before 2012, this number certainly underestimates the incidence of factor XIII deficiency. It is most likely that a systematic evaluation of the number of total cases would confirm a higher incidence.

Thus, our observations emphasize the need to screen for coagulopathy including factor XIII activity also in the absence of pre-operative bleeding symptoms. This approach may influence treatment strategies and help to avoid severe bleeding during or after invasive procedures in patients at risk. In 2012, we, therefore, initiated a screening program for each oncological patient at time of diagnosis. We would like to encourage our colleagues to join the program and to establish a bleeding registry for patients in pediatric oncology. This might provide more resilient data about the prevalence of coagulopathy in pediatric malignancy and may help to improve supportive care strategies.

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