Hemorrhage and thrombosis in acute leukemia

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Patients with acute leukaemias are at high risk of both hemorrhage and thrombosis.

This risk is different according to: 1. the type of leukemia, i.e.: acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL), or acute promyelocytic leukemia (APL); and 2. the phase of treatment, i.e.: onset of the disease, remission induction, consolidation.

Among bleeding complications, of particular importance is the disseminated intravascular coagulation (DIC) syndrome, due to the massive intravascular activation of blood coagulation with consumption of clotting factors and platelets, leading to severe haemorrhages.

Thrombosis of large vessels is a more rare complication, although recent data indicate that it can be a relevant problem at the onset of AML, and during induction chemotherapy in ALL.

PREVALENCE

Acute myelogenous leukemia (AML)

Hemorrhage

During remission induction, the prevalence of life-threatening bleeding is difficult to evaluate for the different descriptive criteria utilised and the incomplete reporting of data. Fatal bleeding at diagnosis and before any chemotherapy is very rare in the modern age. In adult patients with AML, 1% of lethal bleedings on day of admission have been observed, all in the presence of hyperleukocytosis or APL.[1] More substantial data are available on deaths after initiation of treatments. Recent data in patients with AML show a rate of haemorrhagic death of 9.9%, whereas in studies reporting hemorrhage as a contributory cause of death, the rate increases up to 33%. In the MRC 10 trial, the mortality rate for pulmonary or cerebral haemorrhage in the early stages of treatment was 2%, and was associated with M4 and M5 morphology, high initial white cell count and concomitant infections. These data suggest a strong correlation between unresolved infection in the pancytopenic patient and terminal hemorrhage.[1]

During consolidation, patients in complete remission must be considered in a different perspective. Currently post-remission therapy is administered at increased intensity, including protocols for allogeneic or autologous bone marrow transplantation in first remission. Therefore, coagulation abnormalities or blast cell count play a minor role in this phase, with the exception of intercurrent autoimmune thrombocytopenia, persistent thrombocytopenia due to graft failure, and thrombotic thrombocytopenic purpura secondary to bone marrow transplantation. Much more commonly, during consolidation, thrombocytopenia is a direct consequence of myelosuppressive therapy, but concurrent infections may also contribute to the pathogenesis of fatal haemorrhages. The incidence of remission deaths specifically caused by hemorrhage is very low when platelet support is adequate. In AML the cumulative rate from different studies dealing in detail with this specific aspect is 1.5%.[1]

Thrombosis

In AML few data on the thrombotic risk are available. A recent large retrospective study shows a venous thromboembolic event rate of 2.09% at the onset of the disease, with no significant difference between AML and ALL.[2] However, a prospective study demonstrates that, at the onset of leukemia, incidence of thrombosis is greater in AML than in ALL, whereas during treatments, this risk is greater in ALL than in AML.[3]

A prospective analysis conducted in patients admitted to our Center from 2000 to 2005, shows a thrombosis rate in induction of 2.3% in patients with AML (excluding APL) and 10.3% in patients with ALL.

Acute promyelocytic leukemia (APL or AML-M3)

APL typically presents with a life-threatening haemorrhagic diathesis which is particularly severe in the microgranular variant (M3v), with marked hyperleukocitosis. Before the introduction of all-trans retinoic acid (ATRA) in the management of APL patients, fatal haemorrhages caused by the APL-associated coagulopathy were a major cause of induction remission failure, with a prevalence of haemorrhagic deaths in induction of about 10%. The rate of early haemorrhagic deaths was similar in patients receiving heparin, antifibrinolytics, or supportive therapy alone, for the management of the coagulopathy.[4] ATRA has produced a high rate of CR and a rapid resolution of the coagulopathy without causing bone marrow hypoplasia. In non-randomized studies compared with historical controls treated with conventional chemotherapy, APL patients administered ATRA showed a 9% to 20% improvement of the CR rate and reduction of early haemorrhagic deaths. These preliminary findings were confirmed by randomized clinical trials.[5] However, APL patients treated with different combination of ATRA plus chemotherapy still show a prevalence of early haemorrhagic deaths ranging between 2.4% and 6.5%. Prognostic factors for early death are older age and high WBC count.

Acute lymphoblastic leukemia (ALL)

A syndrome characterized by bleeding and thrombosis was first recognized by Priest *et al.,* in children with ALL treated with polichemotherapeutic protocols including L-Asparaginase (L-Ase). Subsequently, these observations have been confirmed: cerebral thrombo-haemorrhagic accidents and peripheral deep vein thrombosis are reported in 2.4 to 11.5 % of children with ALL. In adults, haemorrhage is also the main cause of early death during remission induction in ALL patients treated with an intensive regimen including L-Ase (reviewed in ref. #1)

Recently, 12% rate of thrombo-haemorrhagic events during treatment with L-Ase has been confirmed.[6] In patients prospectively enrolled in our Center from 2000 to 2005, during treatment (including L-Ase), we recorded 10.6% thrombotic events and 3.4% non fatal severe haemorrhage.

PATHOGENESIS

The coagulopathy of acute leukemia.

Abnormalities of the blood clotting system underlying the clinical pictures of DIC are observed in AML, less commonly in ALL. These abnormalities include hypofibrinogenemia, increased FDPs and prolonged prothrombin and thrombin times. These laboratory parameters often become more abnormal upon the initiation of cytotoxic chemotherapy, resulting in severe haemorrhagic complications. The advent of new laboratory tests for hypercoagulation markers clearly show that thrombin generation is a constant finding in acute leukaemia. Particularly important is the detection of the D-dimer, the lysis product of cross-linked fibrin, which definitely demonstrates that hyperfibrinolysis occurs in response to clotting activation in leukaemia.[5]

The advent of ATRA for the remission induction therapy of APL has opened new perspectives in the management of the coagulopathy. Clinicians soon noted the rapid resolution of the bleeding symptoms in patients treated with ATRA. A number of laboratory studies have confirmed the decrease or normalization of clotting and fibrinolytic variables during the first one or two weeks of therapy with ATRA.[5] The beneficial effect on hypercoagulation/hyperfibrinolysis parameters parallels the improvement of clinical signs of the coagulopathy in these patients. The benefit persists when ATRA is given in combination with chemotherapy.

Pathogenetic factors

The major determinants for the pathogenesis of the coagulopathy of acute leukemia are the following: 1. Factors associated with leukemic cells, including the expression of procoagulant, fibrinolytic and proteolytic properties, and the secretion of inflammatory cytokines, 2. Cytotoxic therapy; and 3. Concomitant infectious complications.

Many studies have characterised the procoagulant activity (PCA) expressed by leukaemic cells, particularly *tissue factor*'(TF), the major activator of blood coagulation from normal and pathological tissues, and 'cancer procoagulant' (CP), more typical of malignant tissues. All AML subtypes express significant amount of PCA, with the greatest expression in the M3 type. Measurable PCA amounts are also found in ALL blasts. In AML patients CP levels appear to be related to the phase of the disease.

Leukaemic cells can also express fibrinolytic and proteolytic activities, which are believed to play a major role in the pathogenesis of the bleeding syndrome. However, these activities are lower compared to mature granulocytes. A recent study demonstrates the expression of an annexin II-associated fibrinolytic activity in APL blasts, which appears increased compared to other more immature myeloid subtypes or lymphoid blasts.

Leukaemic cells produce inflammatory cytokines, including TNF-α and IL-1β that increase the prothrombotic and proadhesive potential of endothelial cells. A role for the blast cytokines in the pathogenesis of the acute leukemia coagulopathy was sug-

gested from the findings that leukemic promyelocytes from patients with DIC secreted more IL-1b than APL blasts from patients without DIC.[5]

Anti-cancer therapies can also increase the risk of thromboembolic complications in several ways, i.e.: the release of procoagulants and cytokines from damaged malignant cells; the direct drug toxicity on vascular endothelium; direct induction of monocyte or tumour cell TF; and the decrease in physiological anticoagulants.

Life-threatening bleeding occurs more frequently when patients with acute leukemia have concomitant infections. Some infections are particularly important such as viral (cytomegalovirus, herpes, varicella), bacterial (sepsis due to gram-negative or gram-positive microorganisms), and mycotic (Aspergillus spp). The contribution of infection to bleeding complications is very relevant in gram-negative sepsis, because of the presence of endotoxin on cell wall which possesses pyrogenic, lethal, hypotensive and procoagulant effects.

THERAPY

Platelet transfusions

Prophylactic platelet transfusions therapy represents an essential part of the modern supportive care for patients with acute leukemia. This practice has resulted in a marked decrease in the incidence of bleeding, prolonged survival, and allows for the intensification of therapy. Traditionally, a threshold value of the platelet count below of 20×10^9/L has been used, however, the indication for prophylactic platelet transfusion can be modulated according to the clinical setting. The safety of a stringent prophylactic platelet transfusion policy has been confirmed in comparative, nonrandomized studies and in randomized clinical trials. The Italian multicenter clinical trial in AML showed that a threshold of 10×10^9/L reduced platelet use of 21% without increasing major bleeding complications.[1]

These recommendations do not apply to patients with APL, whose bleeding risk and platelet transfusional requirements remain higher also in the retinoic acid era. Current recommendations for patients with APL suggest that platelets should be transfused to maintain the platelet count above 20×10^9/L in patients not actively bleeding and above 50×10^9/L in patients actively bleeding.

Heparin and antifibrinolytic agents

The role of heparin therapy in the treatment of the coagulopathy complicating acute leukaemia remains uncertain, because its benefit has never been proved by prospective randomized trial. Thus, the routine use of heparin in this condition cannot be presently recommended.

Since increased fibrinolytic and other protease activities have been implicated in the pathogenesis of the coagulopathy, therapeutic regimens including antifibrinolityc agents such as epsilon-aminocaproic acid and tranexamic acid, or protease inhibitors such as aprotinin, have been suggested. However, even most recently published observations fail to demonstrate the occurrence of primary hyperfibrinolysis *in vivo*. The efficacy of tranexamic acid in controlling the haemorrhagic syndrome in APL with a concurrent substantial reduction of the transfusion requirements has been suggested on the basis of results obtained with small series of patients. In addition, it is of great importance to consider the possibility of thromboembolic events, when antifibrinolytic agents are given during ATRA therapy.

All-Trans-Retinoic Acid (ATRA)

ATRA is a differentiating agent able to induce complete remission of APL accompanied by a prompt amelioration of the acute coagulopathy.[5] Some of the mechanisms by which ATRA can interact with the haemostatic system have been elucidated or are currently under investigation. ATRA can interfere with each of the principal hemostatic properties of leukemic cells, including the expression of procoagulant, fibrinolytic and proteolytic activities, and the secretion of inflammatory cytokines, i.e. IL-1β and TNF-α, which affect hemostatic properties of the vascular endothelium and leukocyte.

In addition, ATRA interferes with the hemostatic properties of normal cells including endothelial cells and monocytes. Indeed, besides protecting the endothelium from the procoagulant insults of cytokines, ATRA directly increases thrombomodulin expression by cultured human endothelial cells, and enhances the endothelium fibrinolytic functions, by stimulating tissue-plasminogen activator production. Therefore, ATRA protects the endothelium from fibrin deposition. Finally, relevant is the capacity of ATRA to inhibit the PCA of human monocytes.

It must be noticed that clinical data indicate that, in spite the improvement of the coagulopathy, ATRA has not decreased significantly the rate of early deaths in APL. Furthermore, to the moment, ATRA alone cannot be recommended in the APL microgranular variant (M3v) with hyperleukocytosis, which carries the greatest haemorrhagic risk.

Treatment of thrombosis in ALL

The relative rarity of venous thromboembolism in acute leukaemia patients explains the scanty data published in the literature and the difficulty to set

randomised clinical trials of prophylaxis or therapy of thrombosis in this setting. Today the availability of low molecular weight heparins (LMWH), which show a better safety profile, has greatly improved the treatment of these complications in patients with solid tumours. A protocol with full dose LMWH (200 U/Kg/d) for one month, followed by 75% of the initial dose for other five months, is currently recommended to treat deep vein thrombosis in cancer (with temporary dose reductions or discontinuation, in case of chemotherapy-induced thrombocytopenia). However, there are no studies that have addressed this problem in patients with acute leukemia, who are at higher risk of bleeding, due to the profound and prolonged pan-cytopenias caused by high-dose chemotherapy regimens. For these reasons, it is likely that the use of thromboprophylaxis should be considered, particularly in subjects and therapeutic regimens (i.e. L-Ase) at high thrombotic risk profile.

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