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Effect of Therapeutically Related Drugs on Coagulation-Anticoagulation Balance in Acute Promyelocytic Leukemia

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Abstract

Acute promyelocytic leukemia (APL) usually presents with a series of coagulation-anticoagulation disturbance. Early administration of All-trans retinoic acid (ATRA) can reduce the risk of bleeding, but the potential for thrombosis needs to be addressed in some cases. The role of arsenic agent in correcting coagulation disorder remains to be studied, but oral arsenic agent shows potential advantages in coagulation recovery compared with intravenous agent, and chemotherapy can aggravate the progress of coagulation disease. In addition to early application of ATRA, avoiding invasive procedures and transfusion support can reduce the risk of bleeding. Whether the administration of heparin, thrombomodulin, recombinant factor VIIa or antifibrinolytics reduces the risk of bleeding and thrombosis associated with APL remains to be further explored, and their routine use outside of clinical trials is not recommended. This article reviews the effects of related drugs on coagulation-anticoagulation balance in APL patients.

Keywords

acute promyelocytic leukemia, coagulation, all-trans retinoic acid, chemotherapy, arsenic trioxide

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Introduction

Acute promyelocytic leukemia (APL) is a specific subtype of acute myeloid leukemia (AML) (M3 subtype) in France-America-Britain (FAB) typing, characterized mainly by a specific chromosomal translocation, t(15; 17)(q22; q12) and the formation of a PML-RARα fusion gene. The prognosis of this disease has improved significantly due to the standardization of drugs such as all-trans retinoic acid (ATRA), which has become a curable subtype of acute leukemia without hematopoietic stem cell transplantation.[1,2] However, coagulopathy in APL continues to receive close attention as a major cause of early death (ED).[3] Different therapeutic agents and regimens should consider their impact on the coagulation-anticoagulation balance in APL patients, in addition to targeting the leukemic cells. The study of the effect of APL treatment-related drugs on the coagulation balance can help to select timely and reasonable clinical treatment measures, which can further reduce the occurrence of deaths related to coagulation disorders.

Mechanisms and Clinical Manifestations of APL-Related Coagulation Abnormalities

Leukemic cells themselves can interact with the coagulation system in several ways: activation of coagulation pathways due to the release of procoagulants (eg, cancer procoagulant [CP] and tissue factor [TF]), activation of coagulation pathways and alterations in the fibrinolytic system (fibrinolysis and high expression of membrane-linked protein II, etc). In addition to these factors, endothelial cell damage, reduced platelet count and abnormal function, infections, and inflammatory reactions can also trigger or aggravate coagulation disorders.[4] Due to

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the imbalance of coagulation and anticoagulation, patients with APL can have a variety of clinical manifestations, especially bleeding symptoms occupy the main part. The site of bleeding is mostly skin and mucosa, and severe bleeding occurs mainly in the brain, gastrointestinal tract, and lungs.[5] Thrombosis in APL patients can occur before, during, and after treatment, and may even be a sign of recurrence.[6] Arterial thrombosis in APL patients mainly manifests as cerebral infarction, myocardial infarction, and ventricular thrombosis, while venous thrombosis can occur in the deep veins of the lower extremities, intracranial venous sinuses, and the manifestations of thrombosis and hemorrhage can also occur simultaneously as clinical signs of bleeding and coagulation disorders.[7–11]

Effect of APL Therapeutic Agents on Coagulation-Anticoagulation Balance

ATRA

The efficacy of ATRA in patients with APL has been demonstrated, and a regimen of ATRA combined with other drugs can result in complete remission (CR) rates of 90% and higher and can significantly reduce the relapse rate.[12–14] The mechanism of ATRA is to induce differentiation of promyelocytes to middle and late granulocyte stages. In addition, ATRA plays an important role in improving bleeding problems in APL patients, and a study showed that delayed application of ATRA for APL treatment resulted in severe bleeding events in patients.[15] And delayed ATRA administration beyond 24 h of hospitalization was also a significant predictor of ED in high-risk APL patients.[16] The measurements of coagulation activation markers (thrombin antithrombin [TAT], D-dimer, prothrombin fragment 1 + 2 [F1 + 2] and plasma fibrinopeptide A [FPA]) revealed that ATRA treatment rapidly reduced the procoagulant load of APL tumor cells.[17] An increase in protein C and a decrease in fibrin and vascular hemophilia factor (von Willebrand factor, VWF) hydrolysis after ATRA treatment were consistent with an improvement in clinical symptoms associated with coagulation in APL patients.[18]

The use of ATRA in patients with APL is effective in reducing the risk of severe bleeding, and although there are conflicting claims as to whether it promotes thrombosis, its potential risks are worthy of concern. ATRA may act on the coagulation-anticoagulation system through the following mechanisms: (1) ATRA has a role in APL cell secretion of related cytokines and surface proteins: ATRA decreases APL cell expression of cellular procoagulants (CP and TF) that activate the coagulation cascade and inhibits coagulation pathway activation; ATRA also increases APL cell expression of urokinase-type plasminogen activator (u-PA), tissue-type plasminogen.[9] (2) Major effects of ATRA on vascular endothelial cells and monocytes: ATRA induces the expression of thrombomodulin (TM) in endothelial cells (EC), a membrane receptor that binds to and inactivates thrombin; the protein C/protein S system is then activated by the TM/thrombin complex, a potent anticoagulation mechanism; ATRA inhibits EC and mononuclear phagocyte-exposed tissue procoagulant TF expression; ATRA induces t-PA and a small amount of PAI-1 production by EC and promotes endothelial cell fibrinolytic response; ATRA counteracts the prothrombotic effect of cytokines tumor necrosis factor-α (TNF-α) and interleukin 1b (IL-1b) on EC.[18] (3) ATRA on platelet action: One study investigated the effects of ATRA on platelet function by incubating human platelets with different doses of ATRA and found that ATRA inhibited platelet aggregation, proliferation, clot contraction, and impaired in vivo hemostatic processes and arterial thrombosis after ATRA treatment. ATRA may inhibit platelet function through direct or indirect inhibition of PKCβI/δ, which in turn inhibits platelet function and thrombosis.[19] One study found ATRA to be a promising candidate for patients with glucocorticoid-resistant or relapsing primary immune thrombocytopenia.[20] (4) ATRA for cytokines: it may also increase cytokines that cause endothelial damage such as IL-1b and TNF-a, inducing thrombosis in EC.[17,18,21]

Arsenic Agents

There are two types of arsenic agents currently used in clinical practice, including intravenous ATO and oral arsenic agents (Realgar-Indigo naturalis formula, RIF). Patients with APL who received ATRA-ATO therapy experienced better long-term quality of life outcomes than those who received ATRA with chemotherapy.[22] The main role of ATO is to induce apoptosis and differentiation of leukemic cells, and the survival rate is significantly improved with the application of ATO regimens. The safety and efficacy of oral arsenic in APL has also been demonstrated.[23] However, there is no conclusive evidence on whether arsenic accelerates the recovery of coagulation fibrinolytic abnormalities in APL patients.

Studies have shown that although conventional therapeutic doses of ATO have no effect on platelet aggregation and adhesion function in APL patients,[24] the activity of TF and procoagulant was significantly reduced in ATO-treated APL cells.[25] Also, arsenic dose-dependently induced platelet phosphatidylserine (anionic phospholipids, usually found in cell membranes, are an important component of the activity of endo-factor Xase and plasminogen complex) exposure and particle formation.[26] In a retrospective clinical study on the effect of ATO on coagulation and fibrinolysis in APL patients, compared to ATRA, although TF mRNA expression was downregulated and procoagulant activity (PCA) and TF levels were reduced after ATO treatment, the changes in tPA activity, PC activity and TM antigen content before and after treatment in the ATO group were not significant.[27] Another study also noted no significant difference in the trend of changes in D-dimer and platelet count on days 0-29 in patients with the same baseline levels of fibrin and coagulation markers in the ATO (ATO + ATRA + /no chemotherapy) and non-ATO (ATRA + /no chemotherapy) groups. The median value of activated partial thromboplastin time (APTT) remained within the normal range in

both groups of patients. Fibrinogen (FBG) levels were not significantly different between the two groups on days 0-10 and were significantly different on day 13. However, FBG had returned to normal in both groups. There was a difference in the median PT values between the two groups on days 4 and 7, with the ATO group slightly higher than the non-ATO group ($P < .01$). The application of ATO does not appear to have sufficient potential to accelerate the correction of coagulation and fibrinolytic abnormalities in patients with APL-associated bleeding and clotting abnormalities.[28,29]

In contrast to ATO, RIF has a potentially beneficial effect on the recovery of thrombocytopenia and hypofibrinogenemia in APL patients with non-overt DIC.[30] A study divided 83 APL patients aged 15-59 years into an ATO-ATRA ("ATO" group, n = 38) and RIF-ATRA ("RIF" group, n = 45) and confirmed that there was no difference between the two groups in terms of consumption of component blood, platelet recovery and rate of coagulation correction. However, in 42 patients with disseminated intravascular coagulation (DIC) score of 4, platelet consumption by transfusion was lower in the RIF group than in the ATO group ($P = .037$). In 17 patients with DIC score <4, FBG levels recovered faster in the RIF group than in the ATO group ($P = .028$). The mechanism by which RIF improves coagulation in APL patients is less studied, probably because the main adjuvant component of RIF, tanshinone IIA, inhibits platelet aggregation while enhancing tetraarsenic tetrasulfide-mediated PML-RARα degradation and thus enhancing the therapeutic effect, reducing platelet depletion and significantly improving thrombocytopenia.[31] In addition, tanshinone also improved the decrease in plasma FBG and platelet levels in rabbits with DIC and reversed the decrease in protein C and antithrombin III activity.[32]

Chemotherapy

In APL patients with WBC $>10 \times 10^9$/L, the addition of chemotherapeutic drugs to retinoic acid and arsenious acid is recommended, commonly anthracyclines, anthraquinones, and cytarabine.[1] Chemotherapeutic agents can cause a hypercoagulable state in patients with APL when reducing the leukemic tumor load, thus increasing the risk of coagulopathy in patients.[33] Another related study evaluated and compared coagulation activation indices in two groups of patients, each treated with ATRA alone or chemotherapy alone. The slower decrease in D-dimer, F1 + 2, TAT and FPA levels in patients treated with chemotherapy compared to the ATRA group suggests that chemotherapy is not as effective in addressing DIC in APL patients.[17]

Drugs for the Treatment of APL-Related Coagulopathy

Overview

The most important measures to reduce the risk of bleeding and thrombosis-related death are the early use of ATRA/ATO to control the progression of APL and the reduction or avoidance of invasive procedures during treatment. In addition, platelet counts above 30×10^9/L and FBG concentrations above 100 mg/dL should be maintained by transfusion of fresh frozen plasma, FBG and/or components such as cold precipitation and platelets. Supportive therapy should be continued during induction therapy until clinical signs and laboratory indices of coagulopathy return to normal.[1] In addition to this, heparin, TM, recombinant factor VIIa, tranexamic acid and other drugs are used in specific clinical situations to control the occurrence of bleeding or thrombosis.

Heparin

Low-dose heparin therapy is theoretically indicated for treating patients with DIC, as it inhibits fibrinogenesis and thus prevents the exhaustion of coagulation factors.[34] Low-molecular heparin significantly inhibits the adhesion of APL cells to the vessel wall by regulating the expression of EC adhesion molecules. This property of heparin may be a way to stop excessive coagulation activation and microthrombotic deposition in APL patients.[35] However, it is associated with an increased risk of bleeding in patients with septic DIC, making it less commonly used in this setting (unless significant thrombosis is present). This is despite the fact that 49 patients with APL treated with heparin in one study showed a significant improvement in clinical bleeding symptoms and a significant reduction in the time to normalization of FBG, APTT, PT and time to PLT stabilization.[36] However, its use in this setting was associated with increased transfusion requirements and increased risk of delayed bleeding, without any clear concurrent benefit.[37] Therefore, existing guidelines and consensus generally recommend against the use of heparin in APL on no obvious thrombotic basis.[1]

Thrombomodulin

In anticoagulation therapy, a small Japanese study suggested that human soluble recombinant thrombomodulin (rTM) may help to alleviate the DIC problems associated with APL.[38] Another study reported that rTM exerts its anticoagulant effect by inhibiting thrombin activity through the process of thrombin binding and is usually administered at a dose of 380 u/kg/day for 7 days. rTM has an additional antithrombotic effect by activating the Protein C pathway and releasing Activated Protein C (APC) in blood circulation.[39] rTM treatment improved DIC more significantly and reduced bleeding symptoms in DIC patients compared with heparin treatment. And the incidence of bleeding conditions within 1 week after the start of treatment was lower in the rTM treatment group than in the heparin group (43.1% vs 56.5%, $P = .0487$).[40] Due to the anticoagulant effect of rTM, bleeding is one of the common adverse events of rTM. In Japan, rTM is widely used in patients with coagulopathy during APL induction therapy. In a Japanese study, 49 patients received rTM before starting antileukemic therapy and one patient experienced early death due to hemorrhage, suggesting

that early rTM treatment may lead to a reduction in the rate of bleeding related ED.[41] However, further prospective controlled studies are still necessary and the use of this agent outside of clinical trials has not been recommended.

Recombinant Factor VIIa

The role of prothrombin complex concentrate and recombinant factor VIIa in the treatment of fatal bleeding in APL remains unexplored. Although some reports suggest that recombinant factor VIIa is effective for fatal bleeding in patients with APL,[42,43] they provide a low level of evidence. And, given the potential increased risk of thrombosis,[44,45] the use of these procoagulants for the treatment of severe bleeding associated with APL should be limited to clinical trials.

Antifibrinolytic Drugs

Antifibrinolytic drugs to prevent bleeding in hematologic patients, such as the lysine analogs tranexamic acid and aminohexanoic acid, are common. Although some small trials have demonstrated that tranexamic acid and aminocaproic acid improve fibrinolysis-related markers and reduce the need for platelet and plasma transfusions.[46] However, in a larger study, 67 patients who received antifibrinolytic drugs during induction showed no improvement in transfusion requirements or fatal bleeding compared to 107 patients who received induction only,[47] and whether antifibrinolytic drugs increase the risk of thrombosis and whether they increase the risk of adverse events is unclear.[48]

Conclusion

Early use of ATRA may reduce the risk of bleeding, and although the findings on whether it promotes thrombosis are not uniform, its potential risks are still worthy of concern. The role of arsenic in correcting coagulation disorders remains to be investigated, but oral arsenic demonstrates a potential advantage over intravenous agents in the recovery of coagulation signs, and chemotherapy can exacerbate the progression of coagulopathy. Treatment with ATRA started immediately after diagnosis of APL, and interventions such as avoidance of invasive procedures and transfusion support are effective in reducing the risk of bleeding. Whereas low-dose heparin and antifibrinolytic agents have not shown the ability to improve bleeding risk, TM has shown promise in limited retrospective studies, but further prospective data are needed. Recombinant factor VIIa may have a role in fatal bleeding, but the level of evidence is low. The above interventions also need to be evaluated and other possible interventions explored.

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