The complex nature of the prothrombotic state in acute lymphoblastic leukemia of childhood

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The administration of modern chemotherapeutic regimens for the treatment of acute lymphoblastic leukemia (ALL) in children can be associated with severe venous thromboembolic complications, mostly during the induction of remission (IR) stage. Although diverse factors have been implicated in this hypercoagulable state, intensive E. coli L-asparaginase (L-aspar) administration appears to be paramount, through a decrease in the biosynthesis and activity of natural anticoagulant proteins, sometimes compounded by the presence of inherited prothrombotic risk factors. L-aspar pharmacological interaction with additional agents employed during IR is also of particular relevance;\(^3\) In this respect, a recent study including 336 ALL children during IR therapy demonstrated that the concurrent administration of L-aspar with prednisone, rather than dexamethasone, was associated with almost six times the frequency of thromboembolic episodes (10.4% vs 1.8%).\(^7\) It is now evident that different IR protocols for ALL can lead to different rates of thrombotic complications; differences in drugs and drug sources, dosages, time courses, and administration routes could explain this variation. In the last COALL study, for example, a deep venous thrombosis rate of 2.8% was documented.\(^4\) In contrast, in the PARKAA studies this rate reached 29% and 36.7%.\(^5,6\) In this last report, acquired antiphospholipid antibodies, rather than inherited prothrombotic risk factors, were found to be associated with thromboembolic events.\(^5\) The influence of both, hereditary and acquired disturbances of coagulation in the development of thromboembolic episodes might also depend on the treatment protocol.\(^6\) The design of future research in this field must, therefore, take into account the differences in the drugs administered as one of the variables responsible for thromboembolism during ALL treatment. Additional research findings could further contribute to our understanding of this intricate hypercoagulable state. 1. We have documented an in vitro agonist effect of L-asparaginase on platelets from ALL children,\(^7,8\) raising the possibility of a similar platelet agonist effect in vivo. 2. The administration of vincristine at the same time that L-aspar and prednisone induces apoptosis of malignant lymphoblasts in vivo, with an apoptotic index up to 40%.\(^9\) Apoptosis participates in a numerous group of biological phenomena, including thrombogenesis, probably through tissue factor activation.\(^9\) Apoptosis can also trigger the release of microparticles containing circulating blood-borne tissue factor.\(^9\) 3. The formation of potentially thrombogenic heterotypic complexes has been documented between platelets and mononuclear cells, rendering theoretically possible their formation between platelets and leukemic lymphoid cells. In this context, the finding that activated platelets bind preferentially to mononuclear cells appears relevant.\(^9\) 4. Experimental evidence for the induction of platelet thrombi by bacteria, which frequently invade neutropenic children during IR therapy, has been recently provided.\(^10\) Some of these factors appear to be particularly important: the administration of L-aspar and its complex interaction with natural anticoagulants and with additional chemotherapeutic agents, and the existence of a pool of circulating tissue factor,\(^7\) which could potentially be activated by several circumstances that develop in ALL patients during IR therapy. In addition, the platelet contribution to the development and maintenance of the hypercoagulable state in ALL could be considerable, providing an appropriate membrane surface rich in procoagulant phospholipids, probably carrying circulating tissue factor and, once the platelet becomes activated, exposing high-affinity specific receptors for factors V, VIII, IX, and X.\(^11,12\) Most of the described findings, summarized in Table 1, need to be validated in vivo. New research will continue to add potential etiologies for the genesis and persistence of the prothrombotic state during IR therapy for childhood ALL. The specific combination of disease and drug-related factors that favors the shifting of the hemostatic mechanism towards a prothrombotic mode with clinical thromboembolic manifestations in a particular child remains to be defined.

Table 1. Documented and theoretical prothrombotic risk factors in ALL of childhood.

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<th>Documented and theoretical prothrombotic risk factors in ALL of childhood.</th>
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<tbody>
<tr>
<td>1</td>
<td>Decreased synthesis/activity of natural anticoagulants associated to L-asparaginase administration and inherited prothrombotic risk factors;(^3)</td>
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<td>2</td>
<td>Concurrent administration of prednisone, rather than dexamethasone, and L-asparaginase;(^2)</td>
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<td>3</td>
<td>Dosages, sources, routes of administration, and time courses of both, steroids and L-asparaginase in the different treatment protocols;</td>
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<td>4</td>
<td>Platelet activation by L-asparaginase (in vitro);(^5)</td>
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<td>5</td>
<td>Acquired antiphospholipid antibodies;(^4)</td>
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<td>6</td>
<td>Vincristine and prednisone-induced in vivo lymphoblast apoptosis, potentially leading to tissue factor activation (Tf);(^9,10)</td>
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<td>7</td>
<td>Release of microparticles containing circulating tissue factor (in vitro, Tf);(^9)</td>
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<td>8</td>
<td>Preferential binding of activated platelets to mononuclear cells(^10) (lymphoblasts?), leading to formation of thrombogenic heterotypic complexes (Tf);</td>
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<td>9</td>
<td>Induction of thrombi by bacteria (in vitro, Tf);(^9)</td>
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<td>10</td>
<td>Exposure of high-affinity platelet receptors for factors V, VIII, IX, and X by activated platelets (in vitro, Tf);(^10)</td>
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T indicates theoretical risk factor

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Conflict of Interest

All authors declare that they have no conflict of interest.

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