the pathogen from the immune system and leading to the persistence of infection. Additionally, pathogen-induced coagulation results in microvascular occlusion, tissue damage, and subsequent organ failure, exacerbating the pathogenesis of the infection. Whether coagulation is “good” or “bad” in a given patient is most probably dependent on the specific situation. Localized, limited thrombin and fibrin generation is likely to support the host immune response and to enhance pathogen clearance, whereas uncontrolled, systemic coagulation will result in elevated tissue pathogenesis and worsen patient outcomes.

This multifaceted interaction and interplay between pathogen and the host clotting response highlights the difficulties in treating infection-associated coagulopathies. In any given infection, multiple redundant and overlapping pathways are activated leading to the generation of intravascular thrombi, tissue damage, and organ failure. Therapies that target a single pathway involved in infection-induced coagulation often fail to improve patient outcomes. Moreover, therapies targeting the terminal generation of thrombin fail to differentiate between coagulopathy and hemostasis, often leading to bleeding events and again resulting in poor patient outcomes. Understanding these multiple interactions between pathogen, inflammation, and coagulation is critical to the development of effective therapeutic strategies for the treatment of infection-associated DICs. Ultimately, a successful therapy should be able to uncouple infection-induced clotting from normal hemostasis, protecting the patient from DIC while preserving the ability to respond appropriately to surgery or traumatic injury. As our understanding of the processes involved improves, so does our ability to treat these patients.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


LYMPHOID NEOPLASIA

Comment on Roberts et al, page 861

Genomic precision medicine: on the TRK

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In this issue of Blood, Roberts et al describe a preclinical mouse model of acute lymphoblastic leukemia (ALL) caused by the ETV6-NTRK3 fusion gene.

The mouse leukemias were highly sensitive to the specific tropomyosin receptor kinase (TRK) inhibitor that has recently demonstrated significant clinical efficacy in treatment of pediatric and adult solid tumors with NTRK fusions.

Philadelphia chromosome (Ph)-like ALLs are high-risk leukemias characterized by a similar gene expression to that of BCR-ABL1–positive ALLs. They are caused by somatic genomic events activating the JAK-STAT or ABL signaling pathways. Clinical trials testing the efficacy of adding JAK or ABL tyrosine kinase inhibitors to chemotherapy are ongoing (eg, www.clinicaltrials.gov, #NCT01164163). Among the rearrangements identified in Ph-like ALLs, isolated cases with ETV6-NTRK3 have been reported.

Originally discovered in infantile fibrosarcoma, the ETV6-NTRK3 fusion gene is detected in multiple types of tumors (see figure). The NTRK1-3 genes encode the TRK family of tyrosine kinase receptors that are important for neural development. Other fusion translocations involving any of the TRK receptors are also rarely detected in many solid tumors and cause constitutive activation of the kinase domain and oncogenic transformation. Recent RNA sequencing uncovered NTRK fusions in 8 of 7311 hematological malignancies including acute myeloid and lymphoid leukemias, histiocytic and dendritic cell neoplasms, and multiple myeloma. Thus, oncogenic NTRK fusions are identified in many types of cancers.

The traditional classification of tumors is based on histology and tissue of origin. Because of the remarkable progress in genomic characterization of tumors, a complementary molecular classification of cancer based on causative somatic genetic events has been suggested. Precision medicine drugs target the products of these genetic events regardless of tumor histology. A novel specific inhibitor of all TRK proteins, larotrectinib, has recently shown durable responses in the majority of pediatric and adult patients with TRK fusion positive solid tumors of diverse types. Treatment with larotrectinib has
had a reasonable safety profile. Notably, there were no responses in TRK-negative tumors. These dramatic results in phase 1/2 clinical trials demonstrate the premise of genomic-based precision medicine.

These discoveries raise diagnostic and therapeutic challenges that are fundamental to the new era of precision genomic medicine. Which neoplasms should be analyzed for TRK fusions and what is the preferred methodology? How should the extremely rare patient with a hematologic malignancy with TRK fusion be treated, as the above-mentioned studies included patients with solid tumors only? Because of the rarity of suitable patients, a clinical trial for acute leukemias with TRK fusions is very unlikely.

The preclinical model reported in this issue of Blood demonstrates significant activity of TRK inhibitors against a patient-derived xenograft of ETV6-NTRK3 ALL. In a recent case report of a patient with secondary acute myeloid leukemia with the ETV6-NTRK2 fusion, elimination of the ETV6-NTRK2 clone was observed after 10 weeks of therapy with oral larotrectinib. However, the patient relapsed with leukemic cells carrying other oncogenic proteins, demonstrating the problem of clonal heterogeneity. We believe that based on these preclinical and clinical trials with TRK inhibitors, and on the paradigm of BCR-ABL1-positive ALL, it is reasonable to perform a "single patient clinical trial" with TRK inhibitors for chemotherapy-resistant NTRK fusion–positive hematologic malignancy.

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