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What is the role of novel thrombopoietic agents in the management of acute leukemia?

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A B S T R A C T

The role of novel thrombopoietic agents in the management of acute leukemia is a tale of two molecules, romiplostim and eltrombopag. Both are thrombopoietin (TPO) receptor agonists with somewhat different mechanisms of action. Romiplostim is a peptide TPO receptor agonist that activates the TPO receptor by binding to it just like TPO. Eltrombopag is a nonpeptide TPO receptor agonist that activates the TPO receptor by binding to the transmembrane domain. Both TPO receptor agonists increase platelet counts in healthy humans and in those with immune thrombocytopenia. This review focuses on the potential these agents may have in supportive care of patients with acute leukemia.

Introduction

Three questions arise when considering supportive care for patients with acute myeloid leukemia (AML). First, might a thrombopoietic agent help raise platelet counts in patients during induction or consolidation therapy thereby improving platelet recovery and decreasing bleeding? Second, in patients not receiving chemotherapy for myelodysplastic syndrome (MDS) or AML, can supportive care of this type decrease thrombocytopenia and minimize bleeding and transfusions? And third, do these drugs have an effect on AML blasts? The discussion below revolves around whether the two currently available TPO receptor agonists, romiplostim and eltrombopag, could play a role in the supportive care of patients with AML.

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Romiplostim

Romiplostim (AMG 531, Nplate®, Romiplate®) is known to increase platelet counts in healthy individuals and in patients with immune thrombocytopenia. It consists of an IgG heavy chain into which 4 identical peptides have been added [1]. The peptide contains 14 amino acids that bind the thrombopoietin (TPO) receptor and activate it. Romiplostim binds the distal cytokine homology region of the receptor just like TPO, where it activates the JAK and STAT pathways, the MAP kinase pathway, and a wide range of anti-apoptotic pathways, thereby increasing megakaryocyte growth and viability. Romiplostim is a very potent thrombopoietic agent, with a half-life of 140 h.

Romiplostim should be considered identical to recombinant TPO but with two minor exceptions. First, it binds to the TPO receptor at exactly the same site as TPO (Fig. 1) but with about one quarter of the avidity of recombinant TPO. Second, romiplostim has a half-life about 3-fold greater than recombinant TPO. Neither of these properties has been shown to affect any clinical outcomes and indeed they may compensate for each other.

In healthy humans, romiplostim administration has no effect on the platelet count for the first 5 days after treatment [2]. During this time period, megakaryocytes increase in number, size, and ploidy and then on day 5 start to shed platelets in a very rapid fashion. Romiplostim is a potent stimulator of platelet production and in healthy volunteers platelet counts of 1 or 2 million can easily be attained [2]. So can this molecule stimulate early recovery of megakaryocyte precursors and raise the platelet count in patients with acute leukemia or late stage MDS?

Romiplostim and induction/consolidation chemotherapy in acute leukemia

No study has examined whether romiplostim can raise platelet counts in AML patients, but given its virtual identify with TPO it pays to review prior studies with recombinant TPO molecules. A number of studies with recombinant forms of TPO—pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) and recombinant TPO (rhTPO)—had been conducted many years

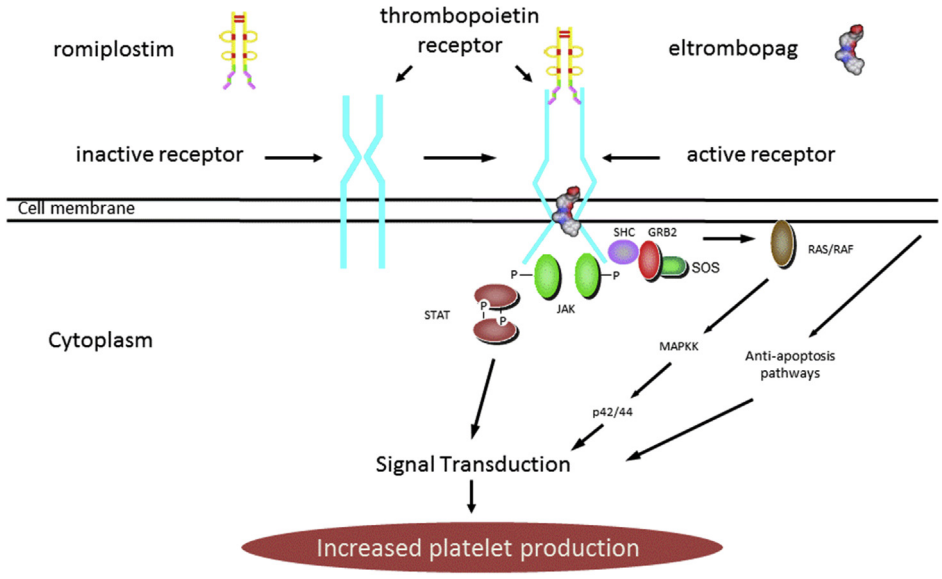

Fig. 1. TPO receptor agonist mechanism of action. Romiplostim and eltrombopag bind the TPO receptor at different sites. Romiplostim binds the TPO receptor at the same distal cytokine homology region as does TPO and eltrombopag binds in the transmembrane region.