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Coagulopathy in Acute Promyelocytic Leukemia: Can We Go Beyond Supportive Care?

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Acute promyelocytic leukemia (APL) is characterized by frequent complications due to a distinct coagulopathy. While advances in treatments have improved long-term survival, hemorrhagic and thrombotic complications remain the most common causes of death and morbidity. Improved understanding of the mechanisms of the coagulopathy associated with APL may lead to therapeutic interventions to mitigate the risk of hemorrhage and thrombosis.

Keywords: APL, ATRA, hyperfibrinolysis, hemorrhage, thrombosis, delayed bleeding

INTRODUCTION

Acute promyelocytic leukemia (APL) is caused by a translocation of the retinoic acid receptor alpha (*RARα*) on chromosome 17, most commonly with the promyelocytic leukemia gene (*PML*) on chromosome 15, which leads to clonal proliferation of promyeloblasts (1). The specific focus of this review is APL with *PML-RARα*, classified by the 2016 World Health Organization (WHO) criteria as a distinct entity apart from rare variants of promyelocytic leukemia (2).

Long-term survival outcomes for APL are now higher than any other acute leukemia as a result of advances such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) (3, 4). For APL patients who survive the first 30 days, over 90% are cured of the disease (4, 5). The increasing use of combined ATRA and ATO for patients with low and intermediate-risk APL has improved long-term cure rates in the disease (6). Nevertheless, death within the first 30 days after diagnosis remains the most common cause of treatment failure (7). Indeed, an updated analysis from the Swedish Acute Leukemia Registry revealed a 25% mortality rate in the first 30 days of therapy, with no improvement from 1997–2008 compared with 2009–2013 (8). Hemorrhage, particularly intracranial hemorrhage, is the most common cause of early death (7–9). The highest risk period for early death and hemorrhagic complications is in the first 4 days of therapy, though almost 50% of early deaths and hemorrhagic complications occur between day 5 and 30 (8, 10–12). Additionally, venous and arterial thrombosis occurs in up to 20% of patients with APL (13–15). Common thrombotic events include deep vein thrombosis, pulmonary embolism, myocardial infarction, and ischemic cerebrovascular events (13–15). The increased risk of both hemorrhagic and thrombotic complications in APL highlights the unique mechanisms that govern the coagulopathy of these patients. Recent work allows us to better understand how current anti-leukemia treatments impact the coagulopathy associated with APL.