blood advances

Deferiprone and idiosyncrasic neutropenia: light and shadow

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Comment on Badawy et al, page XXX

In this issue of *Blood Advances*, Badawy et al[1] address the issue of neutropenia and its associated long-term infection risks in a large cohort of patients treated with deferiprone (DFP) for iron overload.

Iron chelation, for the management of red blood cell disorders, is of global importance, affecting a significant proportion of transfusion-dependent diseases recently impacted by migration fluxes and now constituting major public health problems, for example, thalassemia and sickle cell disease.[2] Historically, injectable deferoxamine (DFO) has been the standard drug of choice for iron chelation, with proven efficacy and a minimal side effect profile,[3] but limited by compliance.[4,5] Introduction of the oral iron chelators DFP, taken 3 times daily, and deferasirox (DFX), taken once daily, in dispersible tablet or film-coated tablet forms, has improved compliance while providing iron chelation efficacy comparable to DFO for mild-to-moderate iron overload.[6,7]

In high iron overload, DFP alone or in combination with DFO or DFX, shows greater improvement in cardiac iron, reduced iron-related cardiac morbidity, and reduced mortality,[6,7] but its use is limited by "black spot," neutropenia.[7]

In a study of patients receiving DFP for nearly 30 years, Badawy et al evaluated the incidence of idiosyncratic neutropenia (IDIN) and severity of infections, according to the absolute neutrophil count (ANC) thresholds.

Using the recent Neutropenia Guidelines,[8] defined as mild (ANC, 1.0×10^9/L to 1.5×10^9/L), moderate (ANC, 0.5×10^9/L to 1.0×10^9/L), severe (ANC, 0.2×10^9/L to 0.5×10^9/L), or very severe/agranulocytosis (ANC, $<0.2 \times 10^9$/L), they found the infectious risk was inversely correlated with neutrophil count. Those with the most serious or lethal events occurred at ANC thresholds of $<0.2 \times 10^9$/L or $<0.1 \times 10^9$/L, respectively.[8]

IDIN is one of the most frequent causes of neutropenia in adults, especially those older than 50 years, as compared with children and young adults,[9] and DPO is among the most common IDINs in hematology.[10]

Given the high rate of sepsis with severe deep tissue infections, for example, pneumonia, septicemia, and septic shock, in approximately two-thirds of adult hospitalized patients with grade 3 or 4 neutropenia[11,12] and paucity of data in the pediatric age group,[13] this study focused on children receiving DFP <17 years of age. In this pediatric group, IDIN-related mortality was 5%, far lower than previously reported rates of 20%.[12,14]

The exact mechanism by which DFP causes neutropenia is not fully understood, but it is hypothesized to result from direct damage to the bone marrow or immune-mediated destruction.[11]

In many cases, drug exposure can decrease granulocyte production by inducing neutrophil apoptosis either by inhibiting cytokines vital for neutrophil development or disrupting the hematopoietic microenvironment and extracellular matrix.[9-12] In other cases, an immune-mediated mechanism has been postulated. Yet, robust evidence, apart from prolonged drug exposure or re-exposure,[9-12] is lacking.

Factors that increase the risk of neutropenia and severe infections in subjects treated with DFP include age >65 years, degree and duration of neutropenia, renal, cardiac, or respiratory failure, systemic autoinflammatory disease, and use of drug combinations.[9-12] Lethal infections were observed in 1 of 2 patients with Blackfan-Diamond anemia (BDA), which has a 10-fold higher risk of agranulocytosis than thalassemia. These findings highlight the importance of the underlying hematological disorder when

considering risk. To that end, for patients with BDA, iron chelation with DFP in the absence of cardiac iron overload should be reserved as a third-line choice.[15,16]

The strengths of this study are its size, the largest cohort of IDIN DFP-treated patients, and its long observation period. Among the limitations is the use of self-reported information, which may underreport events or risk factors (ie, hypersplenism, ethnicity, and duration of neutropenia) or external factors (environmental or social situations) that may affect the degree of neutropenia and the impact of IDIN.

In summary, the findings of Badawy et al have defined low ANC thresholds that predispose patients to severe infection and also recommend a proactive approach to monitoring all patients receiving DFP. This includes (1) strict monitoring of neutrophil values, especially in the first year of treatment; (2) educating patients to self-monitor for fever or other signs of infection; and (3) using broad-spectrum antibiotics and hematopoietic growth factors (particularly granulocyte-colony stimulating factor) in cases of sepsis. These recommendations will have important implications for the use and monitoring of DFP in the postmarketing setting.

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