

LETTER TO THE EDITOR

Drotrecogin alfa activated as a treatment for severe sepsis in pediatric cancer

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Active protein C is an endogenous modulator of both coagulation and inflammation. Imbalanced activation of protein C may occur as a consequence of inflammatory cytokines. A decreased level of activated protein C in patients with sepsis has been implicated as having a key role in determining multi-organ impairment.¹

The availability of a recombinant form of human-activated protein C led to a multi-center, randomized, double-blind, placebo-controlled trial in adults with severe sepsis (PROWESS trial). Publication of these results in 2001 raised the hopes of all physicians who had lost a patient to severe sepsis.² The trial showed that the use of Drotrecogin alfa activated (Drot AA) decreased mortality (19.4% reduction of the relative risk of death), but increased the risk of serious bleeding (3.5% in the treated group vs 2% in the placebo group, $P=0.06$). Pastores *et al.*³ report on a phase-IV, open-label, clinical trial designed for hematopoietic stem cell transplant (HSCT) patients with severe sepsis. The primary end point was to investigate the safety of Drot AA in HSCT patients with severe sepsis assessed as the rate of intracranial hemorrhage and other severe bleeding. However, the authors were unable to complete the trial, which was stopped prematurely due to slow accrual (only seven patients enrolled

in 10 months), when it became clear that achieving the study end points was not feasible.

Pediatric patients represent another group of patients for which the use of Drot AA is still unclear. The safety, pharmacokinetics and pharmacodynamics of Drot AA in children are reportedly comparable to those observed in adults.⁴ Also, there are anecdotal reports of the use of Drot AA in children and neonates with severe sepsis.^{5,6}

Although no exhaustive data on the therapeutic ratio of Drot AA in children are published, the high mortality rate related to severe sepsis induced us to use Drot AA in seven pediatric patients with cancer who met the criteria for severe sepsis, defined as sepsis with acute organ dysfunction.⁷ The patients received Drot AA 24 µg/kg/h by continuous intravenous infusion for 96 h, in addition to standard care. Table 1 summarizes the main clinical characteristics and outcome of the patients. Although five of the seven children survived, the data do not allow us to draw conclusions on the efficacy of the drug. The most significant finding was the absence of minor or serious bleeding complications, despite a high prevalence of thrombocytopenia. As bleeding is the main concern with the use of Drot AA, Pastores *et al.* requested in their paper that other physicians report any observed bleeding episodes or other important side effects of the drug. Although it is not possible to affirm that this serious side effect is rare in children with cancer receiving Drot AA for severe sepsis, we were compelled to report our experience of lack of bleeding.

Table 1 Clinical characteristics and outcome of cancer children who received Drot AA

Case	Age (years)/gender	Neoplasia	Identified germ	Site	Circulating neutrophils (cells/mm ³)	Organ dysfunctions	Coagulative parameters	Bleeding events	Nadir platelets during therapy (cells/mm ³)	Outcome
1	13/F	Bladder rhabdomyosarcoma	<i>Staphylococcus aureus</i>	Blood	6978	Cardiac Respiratory Neurologic	PT 18" aPTT 40"	None	154 000	Alive
2	10/F	Acute myelogenous leukemia (M1)	<i>Staphylococcus coagulase-negative</i>	Blood	60	Cardiac Respiratory	Normal	None	19 000	Alive
3	4/M	Acute lymphoblastic leukemia (1st relapse)	<i>Bacillus</i> spp	Blood	3233	Cardiac Respiratory	Normal	None	8000	Alive
4	1/F	Acute myelogenous leukemia (M7)	None	Lung	460	Hepatic Respiratory	PT 40" aPTT 40.8"	None	8000	Dead from sepsis 3 days post therapy
5	4/M	Neuroblastoma	<i>Candida</i>	Blood	1880	Neurologic Respiratory	Normal	None	9000	Alive
6	9/M	Acute myelogenous leukemia (M4)	<i>Candida kruseii</i>	Lung	70	Respiratory	Normal	None	7000	Alive
7	4/F	Acute myelogenous leukemia – Bone marrow transplant	<i>Enterococcus faecalis</i>	Blood	440	Cardiac Respiratory Hepatic	PT 46" aPTT 44"	None	17 000	Dead from sepsis 8 days post therapy

Abbreviation: Drot AA = Drotrecogin alfa activated.

Careful assessment of the risk/benefit ratio is mandatory before the introduction of 'new drugs' into clinical practice. Trials with end points of mortality in children with severe sepsis are very difficult to perform because of the lower rate of sepsis and sepsis-related mortality in this patient group. Many clinicians use as yet unproven medical interventions because they feel that the risk of waiting for clearcut evidence could result in loss of life. This occurs particularly in clinical settings such as sepsis in immune-suppressed patients, where the extreme severity of the condition gives the physician clinical and ethical authorization to use a drug whose safety/efficacy profile has not been clearly established. Pediatric oncologists often experience the frustration of controlling the malignancy, but losing the cancer patient to sepsis. Such phenomena may lead to the so-called 'boomerang effect' frequently seen when new therapeutic agents, not carefully investigated, are available.

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