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Commentary

# Radiation Sensitization of Leukemic Cells for Low Dose Total Body Irradiation

Einsley Janowski, Anatoly Dritschilo*

*Department of Radiation Medicine, Georgetown University Medical Center, Washington, DC 20057, United States*

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The treatment of pediatric leukemias has been developed through sequential clinical trials designed to improve patient survival and preserve quality of life (Brochstein et al., 1987). A patient's clinical and biological features are predictive of risk of relapse and determine the aggressiveness of the prescribed clinical treatment protocol. Patients determined to be at high risk for recurrence undergo chemotherapy and total body irradiation (TBI) in the preparative regimen for bone marrow transplantation. Such personalization of treatment has resulted in improved survival. While the 5-year overall survival of pediatric leukemia patients ranges from 60–90% (Allemani et al., 2014), children who experience bone marrow relapse have a three year event free survival of only 20%, supporting the need for further improvements (Gaynon et al., 2006).

Leukemic cells are very sensitive to radiation induced apoptosis, but the magnitude of the TBI radiation dose is dictated not only by the need to control tumor cells, but also to respect normal tissue tolerances of critical organs. Dose dependent late-effects of TBI are of particular concern in the treatment of pediatric patients. In addition to acute pulmonary, cardiovascular, hepatic, and renal toxicities, treatment of children can result in endocrinopathies, neurocognitive impairment, growth disturbances, cataract formation and secondary malignancies as delayed effects (Silverman, 2014). Thus, pediatric clinical protocols focus on reducing or eliminating radiation; however, multiple clinical trials have shown that including TBI is more effective than chemotherapy alone, and even minor reductions of TBI dose have resulted in more relapses (Shi-Xia et al., 2010; Clift et al., 1998).

Although leukemias are generally considered radiation sensitive diseases, the clinically acceptable TBI doses are within tolerance of critical structures and may be insufficient for patient cure. Uckun's characterization of B-cells from recurrent leukemic patients as “radiation resistant” may be viewed in the context of such surviving malignant cells following exposure to conventional doses of TBI (Uckun et al., 2015). The high-risk B-precursor acute lymphoblastic leukemia (BPL) patients experience a high rate of relapse after conventional therapies and may benefit from innovative personalized treatment strategies based on an understanding of molecular genetics and pathogenesis of leukemias (Shi-Xia et al., 2010).

The development of a cancer specific radiosensitizer, to allow TBI dose reduction and to increase treatment effectiveness, is a highly desired goal for leukemia treatment. To this end, Uckun and colleagues report that CD19L-sTRAIL preferentially kills leukemic stem cells from B-cell precursor ALL patients and enhances the killing effects of low dose TBI (Uckun et al., 2015). Furthermore, survival benefit, safety and efficacy of the combination treatment are demonstrated in proof-of-concept experiments in a xenograft animal model. Thus, sensitization of B-precursor ALL by the combination of radiation and the CD19L-sTRAIL fusion protein has potential for improving efficacy of treatment and allowing reduction in the radiation dose used for TBI. Although the effectiveness of TRAIL targeted therapy has yet to be demonstrated in clinical trials, recombinant protein therapies show promise in solid tumor clinical applications for targeted cancer treatment. Uckun's proposal to include CD19L-sTRAIL in the pre-transplant TBI regimens for patients presenting with very high risk BPL is a rational and innovative translational goal.

## Conflicts of Interest

The authors declared no conflicts of interest.

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* Corresponding author.

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