

## Editorial

# Does shining a spotlight on XIAP deficiency bring the role of allogeneic HCT into better focus?

Rebecca A. Marsh, MD Cincinnati, Ohio

**Key words:** XIAP, XIAP deficiency, X-linked lymphoproliferative disease, X-linked lymphoproliferative disease type 2, XLP, XLP2, X-linked inhibitor of apoptosis, hematopoietic cell transplantation, HCT, inborn error of immunity

The current issue of the *Journal of Allergy and Clinical Immunology* contains an important article by Yang et al titled “Phenotype, genotype, treatment, and survival outcomes in patients with X-Linked inhibitor of apoptosis deficiency.”<sup>1</sup> The authors of this article undertook a much needed and practical effort to study the entire literature on recorded patients, spanning the initial discovery of X-linked inhibitor of apoptosis (XIAP) deficiency in 2006<sup>2</sup> through 2020. They summarized the data on a total of 167 patients from 117 families and were able to shine a spotlight to bring several clinical prognostic points regarding XIAP deficiency into better focus. Can these data be used to help answer the most difficult question raised by patients, families, and clinicians alike regarding the role of allogeneic hematopoietic cell transplantation (HCT)?

The question of allogeneic HCT in XIAP deficiency is a difficult one. Since the initial report of XIAP deficiency,<sup>2</sup> it has been clear that patients may develop life-threatening complications of immune dysregulation. XIAP has several cellular functions, including regulation of apoptosis, mediation of NOD1/2-induced activation of nuclear factor- $\kappa$ B signaling, and regulation of TNF receptor signaling and NLRP3 inflammasome function among others.<sup>3</sup> The most common disease manifestations of XIAP deficiency are hemophagocytic lymphohistiocytosis (HLH) and inflammatory bowel disease (IBD). Other complications include splenomegaly, hypogammaglobulinemia, recurrent fevers, infections, hepatitis, arthritis, uveitis, skin abscesses and nonabscess skin problems, and other less common clinical problems.<sup>3</sup> There is no standard curative or preventive treatment for patients with XIAP deficiency aside from allogeneic HCT. Treatment is generally symptomatic and based on disease manifestations and symptoms, which can be refractory.

In the original discovery cohort reported by Rigaud et al in 2006, 4 of 12 patients with XIAP deficiency had died at the time of publication.<sup>2</sup> Deaths occurred within a wide range of ages from 0.5 to 40 years and were related mainly to complications of

HLH.<sup>2</sup> An important subsequent comparison of patients with XIAP deficiency and SAP deficiency by Pachlopnik Schmid et al demonstrated that 5 of 22 patients with XIAP deficiency who developed HLH died and 3 of 5 patients with colitis died.<sup>4</sup> These and other outcomes data could be interpreted to suggest that all patients with XIAP deficiency should be considered for curative treatment with allogeneic HCT. However, some patients with XIAP deficiency have relatively mild phenotypes, and slightly more than half of surviving patients reported by Pachlopnik Schmid et al were clinically well without any treatment at the time of publication of their article.<sup>4</sup> To further complicate matters, patients with XIAP deficiency are at particularly high risk of mortality following allogeneic HCT. Patients fare poorly with fully myeloablative conditioning regimens, and murine studies and clinical observation both demonstrate that XIAP deficiency confers increased risk of severe graft-versus-host disease.<sup>5-8</sup>

Patients with XIAP deficiency would ideally be risk-stratified soon after diagnosis to determine who should be optimally considered for allogeneic HCT versus who should be followed initially with conservative medical management. There are many challenges surrounding outcome stratification, and it is always difficult to compare outcomes between conservatively managed patients and those treated with allogeneic HCT, given that patients presenting at a young age with severe phenotypes tend to be the patients most often considered for allogeneic HCT. The article by Yang et al<sup>1</sup> provides some aggregate insights. First, survival rate was comparable among conservatively treated patients (80%-91%) regardless of HLH, IBD, both HLH and IBD, or other phenotype (Table I),<sup>1</sup> implying that consideration of allogeneic HCT should not be limited to only certain indications such as HLH. Again, this should be tempered with the knowledge that younger patients with more severe phenotypes were more likely to be offered allogeneic HCT. Second, survival was significantly worse for conservatively treated patients who presented before the age of 5 years, with approximately 20% mortality by age 10 years,<sup>1</sup> suggesting that patients presenting at younger ages may be optimally treated with allogeneic HCT. Third, a subset of conservatively treated adult patients had a distribution of disease manifestations and outcomes similar to that of the entire group, but survival was worse for patients who continued to develop new manifestations of XIAP deficiency in adulthood (ie, only 33% at age 30 years).<sup>1</sup> Treatment of patients who continue to develop new manifestations over time may optimally include HCT.

Lastly, neither type of genetic variant nor amount of protein expression was found to predict outcomes. Yang et al<sup>1</sup> found no clear genotype-phenotype correlations other than association of absent protein with development of splenomegaly at younger ages.<sup>1</sup> Residual protein expression was thoroughly shown to not confer a better prognosis in terms of other manifestations or outcomes, although there was a trend toward earlier age of onset

From the University of Cincinnati and Cincinnati Children's Hospital Medical Center, Cincinnati.

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Corresponding author: Rebecca A. Marsh, MD, Cincinnati Children's Hospital, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: [Rebecca.marsh@cchmc.org](mailto:Rebecca.marsh@cchmc.org).

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**TABLE I.** Outcomes of patients treated conservatively (without allogeneic HCT)<sup>1</sup>

| Phenotype    | No. of patients | Survival    | Median age            | Median time after diagnosis |
|--------------|-----------------|-------------|-----------------------|-----------------------------|
| HLH (no IBD) | 54              | 49/54 (91%) | 10 y (range 0.2-39 y) | 4 y (range 0-27 y)          |
| IBD (no HLH) | 20              | 16/20 (80%) | 17 y (range 1-39 y)   | 14.5 y (range 0-30 y)       |
| HLH and IBD  | 10              | 8/10 (80%)  | 10 y (range 3-32 y)   | 6.7 (range 1.6-22 y)        |
| Other        | 25              | 21/25 (84%) | 16 y (range 2.3-46 y) | 14 y (range 1-42 y)         |

**TABLE II.** Outcomes of patients treated with allogeneic HCT reported before or after 2015<sup>1</sup>

| Time period of report | No. of patients | Phenotype(s)                                                                                    | Median age at HCT*   | Overall survival at 1350 days following HCT | Median time after HCT*  |
|-----------------------|-----------------|-------------------------------------------------------------------------------------------------|----------------------|---------------------------------------------|-------------------------|
| 2006-2014             | 28              | With HLH (n = 18)<br>With IBD (n = 5)<br>With HLH + IBD (n = 4)<br>Asymptomatic (n = 1)         | 5 y (range 0.7-19 y) | 41%                                         | 330 d (range 13-1387 d) |
| 2015-2020             | 22              | With HLH (n = 12)<br>With IBD (n = 6)<br>With HLH + IBD (n = 3)<br>With aplastic anemia (n = 1) |                      | 89%                                         |                         |

\*Data applies to all patients in both time frames.

in patients with absent protein.<sup>1</sup> These data are immensely important, and observations about type of pathogenic variant or resulting protein expression should not weigh heavily as part of consideration of HCT.

Yang et al<sup>1</sup> also confirm with aggregate data that patients with XIAP deficiency are generally at high risk of allogeneic HCT complications and historical outcomes have been suboptimal. An indication of HLH, active HLH, and use of a fully myeloablative conditioning regimen in patients with HLH adversely affected HCT outcomes.<sup>1</sup> Encouragingly, however, Yang et al<sup>1</sup> noted that the 5-year estimated survival rate following allogeneic HCT was almost 90% in patients reported in 2015-2020 compared with 41% in patients reported in prior years (Table II).<sup>1</sup> Another recent sizable report from Japan in 2021 also indicates higher survival rates of 85% (n = 26).<sup>9</sup> These data, plus a recent observation of greater than 90% survival in patients with XIAP deficiency who did not develop acute graft-versus-host disease,<sup>6</sup> support optimism regarding allogeneic HCT in the current era. The survival estimates for conservatively treated patients and patients who have received a transplant do not account for disease morbidity associated with long-term symptomatic XIAP deficiency or the impact of possible long-term morbidity that can be associated with allogeneic HCT complications. Future prospective studies are required to better quantify quality of life and freedom from medical interventions in survivors who are treated conservatively or with allogeneic HCT.

In all, Yang et al<sup>1</sup> have contributed a practical and valuable summary of more than a decade of clinical experience from the literature. The data and analyses bring several clinical observations

into better focus and will serve to improve the care of patients affected by XIAP deficiency.

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