

POSTER PRESENTATION

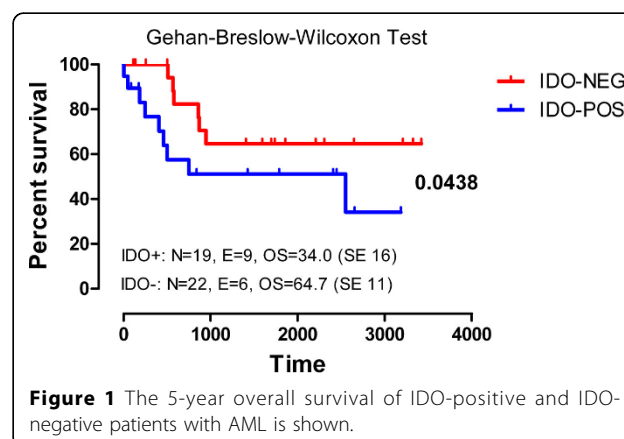
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Indoleamine 2,3-dioxygenase-1 (IDO1) expression by childhood acute myeloid leukemias inhibits T-cell production of IFN- γ and confers an unfavorable prognosis

Sergio Rutella^{1*}, Valentina Folgiero¹, Perla Filippini¹, Valentina Bertaina¹, Riccardo Masetti², Marco Zecca³, Giuseppina Li Pira¹, Giovanni F. Torelli⁴, Anna Maria Testi⁴, Alice Bertaina¹, Andrea Pession², Franco Locatelli^{1,5}

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Indoleamine 2,3-dioxygenase 1 (IDO1) degrades tryptophan into kynurenine (KYN) and other immune suppressive molecules that inhibit effector T cells and promote regulatory T-cell differentiation. We have previously shown that IDO1 mRNA and protein are detectable in blast cells from 52% of adults with newly diagnosed acute myeloid leukemia (AML). Herein, we investigated IDO1 expression and function in 41 children with AML (median age=10 years, range 1-17). In 20/41 cases, leukemia blast cells up-regulated IDO1 after in vitro challenge with IFN- γ . Of interest, microenvironmental IFN- γ was higher in IDO(pos) compared with IDO(neg) patients. In line with these results, bone marrow (BM)-resident T cells produced more IFN- γ , but not IL-4 or IL-17, compared with T cells from normal BM samples. KYN levels significantly increased in supernatants of IFN- γ -stimulated AML cells (21.0 μ M/L, range 6.1-36.0) compared with unstimulated cultures (0.85 μ M/L, range 0.4-1.7; $p=0.0022$), in parallel with tryptophan consumption (2.95 μ M/L, range 1.0-37.0, after challenge with IFN- γ compared with 38.1 μ M, range 18.2-50.0, in unstimulated cultures; $p<0.0001$). In a mixed tumor cell lymphocyte culture, AML blasts primed with IFN- γ inhibited Th1 cytokine production by allogeneic CD8+ and, to a lesser extent, CD4+ T cells, while enhancing Th2 cytokine release. The provision of D, L-1-methyl-tryptophan (1MT), an IDO inhibitor, to T-cell/AML co-cultures partially restored IFN- γ production by both CD4+ and CD8+ T cells. Furthermore,



IDO-expressing AML blasts inhibited NK-cell degranulation, as measured through CD107a expression. Finally, 5-year overall survival was significantly better for IDO(neg) patients (34 months) compared with IDO(pos) ones (64.7 months; $p=0.0438$; Figure 1). In conclusion, IDO suppresses Th1 responses/NK activity and may portend an unfavorable prognosis in childhood AML.

Authors' details

¹Pediatric Hematology/Oncology, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. ²Pediatric Hematology/Oncology "Lalla Seràgnoli", University of Bologna, Bologna, Italy. ³Pediatric Hematology/Oncology, IRCCS Fondazione San Matteo, Pavia, Italy. ⁴Hematology, University La Sapienza, Rome, Italy. ⁵Pediatrics, University of Pavia, Pavia, Italy.

¹Pediatric Hematology/Oncology, IRCCS Bambino Gesù Children's Hospital, Rome, Italy

Full list of author information is available at the end of the article

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