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636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Epigallocatechin-3-Gallate (EGCG) Ameliorates Ineffective Hematopoiesis of Myelodysplasia Syndrome (MDS)

Fernanda Isabel Della Via[1], *Karla Priscila Ferro, PhD*[2], *Guilherme Rossi Assis-Mendonça, gui.rossiam@gmail.com*[3], *Irene Santos, PhD*[4], *Nádia Ghinelli Amôr, PhD*[4], *Fernando Vieira Pericole*[5], *Marisa Claudia De Prax, PhD*[6], *Sara Teresinha Olalla Saad, MD*[4]

[1] Hematology and Transfusion Medicine Centre - Hemocentro, University of Campinas, Campinas, BRA
[2] Hematology and Transfusion Medicine Center - University of Campinas / Hemocentro - UNICAMP, Campinas, São Paulo, Brazil, Campinas, Brazil
[3] Department of Pathology, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, SP, Brazil, Campinas, Brazil
[4] Hematology and Transfusion Medicine Center - University of Campinas/Hemocentro-UNICAMP, Campinas, Brazil
[5] Hemocentro-Unicamp, Campinas, Brazil
[6] Hemocentro-Unicamp, Campinas, Brazil

Epigallocatechin-3-gallate (EGCG) is a gallate ester obtained by condensation of gallic acid with the (3R)-hydroxy group of (-)-epigallocatechin, extracted from green tea, exhibiting beneficial effects as an apoptosis and cell differentiation inducer helping counteract uncontrolled proliferation and impaired differentiation characteristic of leukemia and myelodysplastic syndrome. Clinical trials in patients with chronic lymphoid leukemia, low grade B-lymphomas and acute myeloid leukemia with myelodysplasia related changes were carried out showing positive results. This study aimed to evaluate the *in vivo* effect of EGCG in a mice model of myelodysplastic syndrome (NHD13 mice). B6.SJL-PtprcaPep3b/BoyJ mice (PepBoy) received 9,5Gy irradiation followed by transplantation of bone marrow cells from NUP98-HOXD13 mice by i.v. caudal vein injection; disease establishment was confirmed at day 15 by blood cytopenia. To assess the EGCG effects on MDS, 10-week-old female NUP98-HOXD13 mice (NHD13 $^{+}$) and their littermate WT mice (NHD13 $^{-}$) were treated for 4 weeks with EGCG (50mg/Kg/day 5x/week i.p.) or vehicle. The animals were then sacrificed, and bone marrow and spleen were obtained for flow cytometry and histology analyses. Automated hematological counts and clinical biochemistry parameter analysis were done. After signing the written informed consent, a 71-year-old man diagnosed with high-risk MDS, with 9% blasts in the bone marrow, underwent a daily oral 800mg EGCG treatment. This study was approved by the Ethical Committee of University of Campinas and by the National Research Ethics Committee (**CAAE:** 40656720.5.0000.5404). During this period, the patient underwent weekly clinical assessments and laboratory studies to monitor any potential toxicity. Peripheral blood samples were obtained before and after treatment to observe any alteration in cell counts and immune cell composition. Before treatment, NDH13 $^{+}$ exhibited a reduction in number of leukocytes, platelets, and hemoglobin levels, in accordance with the literature. EGCG treatment ameliorated hematological parameters, showed by increased leukocyte numbers (monocytes and neutrophils) and platelets with no signals of liver and kidney toxicity detected by histology and serum biochemistry. Untreated mice showed increased osteoprogenitor, osteoblast and endothelial cells in the bone marrow, corroborating the literature. EGCG treatment did not alter the frequency of these cells, HSC or immature cells (CD34 $^{+}$ or CD117 $^{+}$). However, EGCG induced extramedullary hematopoiesis in spleen and no changes in the percentage/frequency of Foxp3 $^{+}$ regulatory T cells (CD4 $^{+}$CD25 $^{+}$ and/or CD4 $^{+}$FOXP3 $^{+}$). Additionally, the patient treated by ECGC for one month exhibited reduction of regulatory T cells CD4 $^{+}$CD25 $^{+}$ and CD4 $^{+}$FOXP3 $^{+}$, and increased CD8 $^{+}$ T cells (CD3 $^{+}$CD8 $^{+}$) and *natural killer* cells (CD16 $^{+}$CD56 $^{+}$) accompanied by increased mature leukocytes (monocytes and neutrophils), with no changes in hemoglobin and platelet number. Our initial findings indicate that EGCG induces improved hematological parameters in MDS and might shift immune cells to a more cytotoxic phenotype. The extramedullary hematopoiesis observed in mice may be due to reduction of CXCR4 in bone marrow cells, as previously described by our group. In summary, EGCG might be a promising adjuvant in the treatment of MDS. Further research and clinical studies are warranted to validate and fully explore EGCG therapeutic benefits.

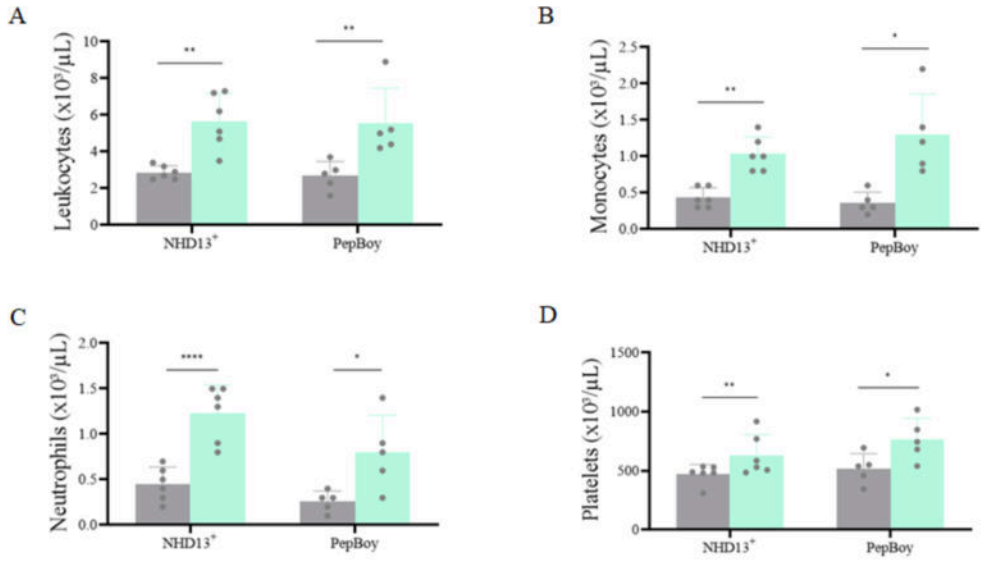
Fig1a EGCG ameliorates NHD13 and transplanted mice hematological parameters. At the end of the EGCG treatment (50mg/kg/day i.p) or vehicle (Ctrl), NHD13 $^{+}$ and transplanted (PepBoy) mice were bled from the retro-orbital plexus. EGCG induced an increased the number of leukocytes (**A**), monocytes (**B**), neutrophils (**C)** and the number of platelets (**D**) using

the CELL-DYN Emerald Hematology System counter. EGCG represented by the green column, and the vehicle by the gray color. Statistical significance (*Mann-Whitney* test) is indicated; n=6 per group.

Fig1b. EGCG improved the immune system of HR-SMD patient. A 71-years-old man with HR-SMD received EGCG treatment (800 mg/Kg/day) for 30 days. Peripheral blood counts were evaluated at day 0 and day 30. EGCG ameliorated hematological parameters - increased mature leukocytes (A) - monocytes (B) and neutrophils (C), with no changes in hemoglobin (D) and platelets

Disclosures Vieira Pericole: *Astra Zeneca:* Speakers Bureau; *Janssen:* Speakers Bureau; *Takeda:* Speakers Bureau; *Sanofi:* Speakers Bureau; *Pfizer:* Speakers Bureau; *Amgen:* Speakers Bureau; *Adium:* Speakers Bureau. **Saad:** *FAPESP Sao Paulo state foundation:* Research Funding.

EGCG ameliorates the hematological parameters of NHD13 and transplanted mice



EGCG improve the immune system of HR-SMD patient

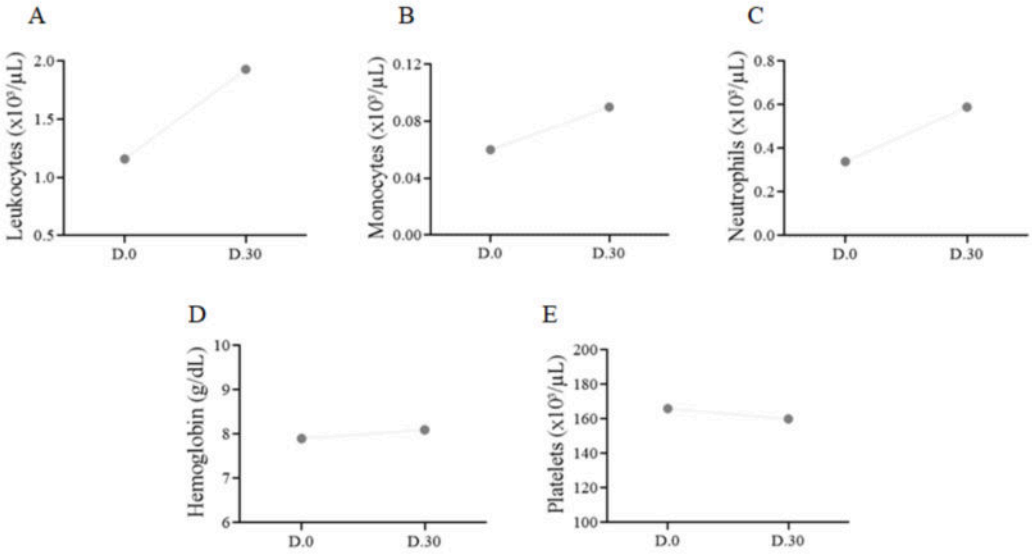


Figure 1

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