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PARP inhibitors are deleterious during human erythropoiesis

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PARP inhibitors (PARPi) are currently used to treat ovarian and breast cancers. By inhibiting DNA damage repair function of PARP enzyme in homologous recombination-deficient cancer cells, such as *BRCA1/2* mutated cells, PARPi induce apoptosis through synthetic lethality. Despite the significant clinical benefit in patients, hematological side effects have been observed, with more than 25% of patients treated by the PARPi Olaparib developing a severe anemia within 3 months, reversible upon treatment arrest.

The objective of this study is to explore the effects of PARPi on erythropoiesis in order to understand how the treatment can induce anemia. To explore this question, CD34+ progenitor cells from leukapheresis were cultured *in vitro* with several doses of olaparib.

First, the levels of PARP1/2 – both being inhibited by Olaparib- have been quantified during erythroid differentiation in liquid culture. We found very minimal PARP1/2 protein expression in CD34+ progenitors and an increase in their expression during the early stages of erythropoiesis. After 7 days of culture, whereas PARP1/2 expressions did not fluctuate with olaparib, global PARylation decreased, confirming inhibition of PARP activity. Clonogenic assays performed with increasing concentrations of the PARPi revealed no difference in the generation of granulocytic, monocytic, erythroid or megakaryocytic colonies indicating that olaparib does not have major effect at the progenitor level. Erythroid liquid cultures showed

that olaparib significantly inhibits cell proliferation in a dose-dependent manner, particularly at late stages of maturation. In parallel, we investigated the erythroid differentiation using the cell surface markers CD36, GPA, Band3 and α4-integrin. Surprisingly, our results showed that olaparib induced an acceleration of differentiation in a dose-dependent manner from D7 of culture. All these observations were also validated after cell sorting of different erythroid population (CD36+GPA- and CD36+GPA+). Finally, we observed a slight increase of apoptosis at late maturation stages, suggesting that olaparib induces cell death of more mature cells.

Our study shows that Olaparib has a dose-dependent deleterious effect on erythroid lineage by limiting proliferation and accelerating differentiation, which may partly explain the anemia observed upon treatment. Ultimately, this study will allow the identification of risk factors for the development of anemia, preventing its occurrence.