

COMPARATIVE STUDIES BETWEEN ERYTHROPOIETIN (EPO) AND PBI-1402, A NEW ERYTHROPOIESIS-REGULATING AGENT (ERA), ON MURINE CANCER MODELS



PROMETIC

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Abstract

Background: PBI-1402 is a first-in-class novel orally active compound which reduces the need for transfusion and increases hemoglobin (Hb) level and red blood cell count (RBC) in chemotherapy-induced anemia (CIA) patients. PBI-1402 promotes the production of erythrocytes by a mechanism of action which is distinct from erythropoietin (EPO). This mechanism involves differentiation of earlier progenitor stem cells (CFU-GEMM) than those affected by EPO (BFU-E, CFU-E).

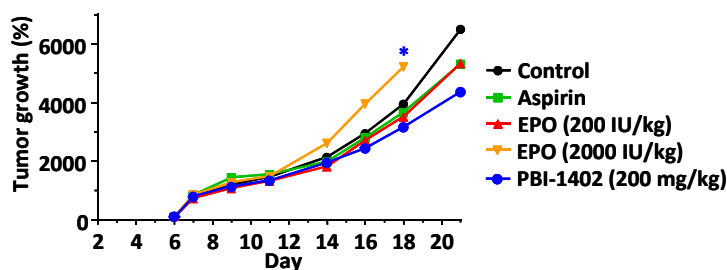
Aim: The objective of this study was to compare the effect of PBI-1402 and EPO on modulation of tumor growth.

Methods

P815 cells (a DBA/2 (H-2d)-derived mastocytoma) and Lewis Lung carcinoma (LL-2) cells express the EPO receptor and the PBI-1402 receptor on their cell surface. At day 0, 5×10^5 viable P815 cells or 0.5×10^5 LL-2 cells were subcutaneously injected to produce localized tumors in 6- to 8-week old DBA/2 mice or C57BL/6 mice, respectively. Mice were then treated every day with oral administration of vehicle (negative control), aspirin (positive control for P815, 50 mg/kg) or PBI-1402 (200 mg/kg) or gemcitabine (positive control for LL-2, 50 mg/kg i.p. once a week) or EPO (200 IU/kg or 2000 IU/kg, s.c. tiw for P815 or once a week for LL-2). Mice were sacrificed at day 21 (P815) or day 26 (LL-2).

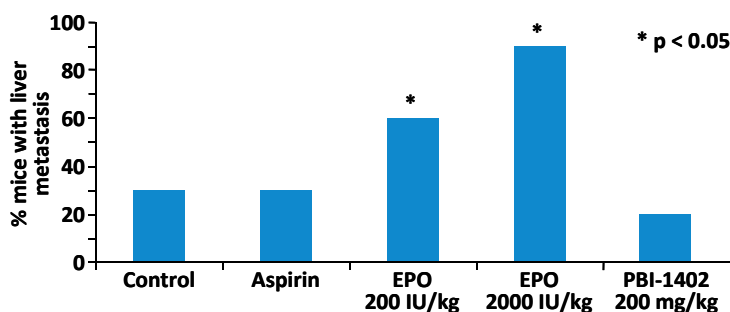
Results

PBI-1402 reduces P815 tumor growth while EPO increases it.



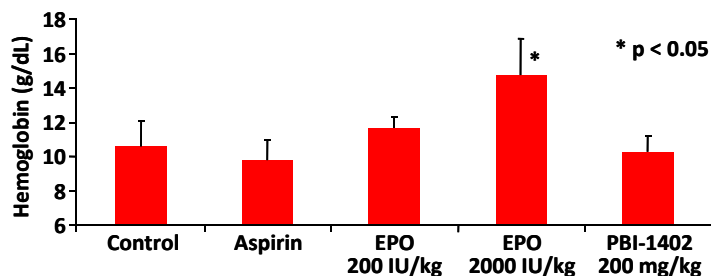
* Exacerbation of cancer growth by EPO.
Four animals treated with EPO (200 IU/kg) tiw died before day 21.

EPO increases the percentage of mice bearing liver metastasis while PBI-1402 reduces it.

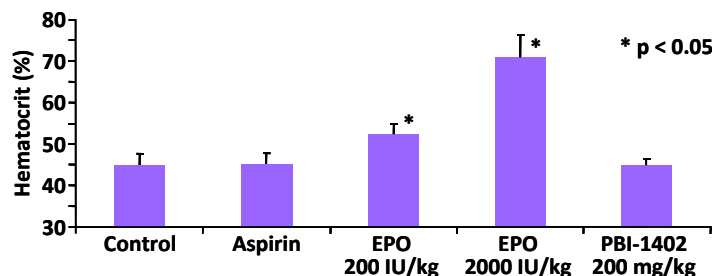


* p < 0.05

EPO treatment overshoots hemoglobin production and hematocrit level while animals treated with PBI-1402 remain within normal values.

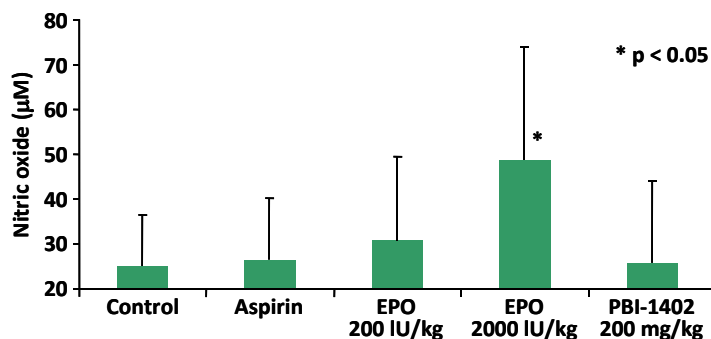


* p < 0.05



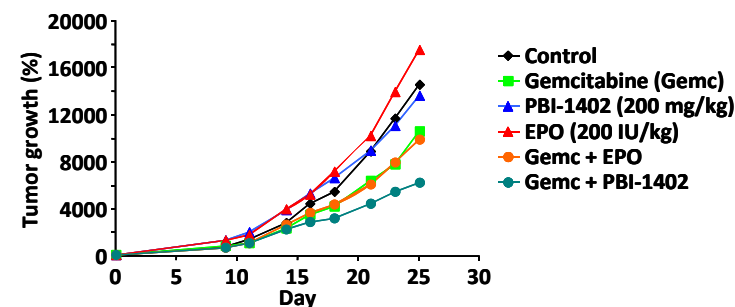
* p < 0.05

EPO increases serum nitric oxide (NO). PBI-1402 has no effect on NO.



* p < 0.05

EPO increases LL-2 tumor growth but has no effect in combination with gemcitabine. PBI-1402 has no effect on LL-2 tumor growth but induces a synergistic inhibition of tumor growth in combination with gemcitabine.



Conclusion

PBI-1402 is safe for use in cancer.

- Novel mechanism of action (non-EPO MoA).
- **No hemoglobin level overshoot. Decreased risk of thrombotic events.**
- **Anticancer activity: tumor growth inhibition, reduction of metastasis, synergistic activity in combination with chemotherapy.**