

Oral treatment with PBI-1402 increases hemoglobin level and red blood cell count: A novel approach to treating chemotherapy-induced anemia



Lyne Gagnon¹, Jean Barabé¹, Christopher Penney¹, Denis-Claude Roy², Vladimir Kovčič³, Snežana Bošnjak⁴ and Pierre Laurin¹

1. ProMetic BioSciences Inc., Laval, Québec, Canada H7V 5B7
2. Hôpital Maisonneuve-Rosemont, Montréal, Québec, Canada H1T 2M4
3. Clinical Hospital Centre Bezanijiska Kosa, Belgrade, Yugoslavia
4. Oncologic Intensive Care Unit and Clinical Pharmacology, Institute for Oncology and Radiology of Serbia, Belgrade, Yugoslavia

Abstract

Background: PBI-1402 is a novel orally active low molecular weight synthetic compound with erythropoiesis stimulating activity. Furthermore, a clinical phase I study showed that PBI-1402 induced a significant increase (100%, $p < 0.0001$, compared to placebo) of relative and absolute reticulocyte count in healthy volunteers after 21 days of oral treatment and was devoid of significant side effects.

Outcomes: The objectives of this clinical phase Ib/II trial were to study the safety and tolerability of PBI-1402 and to assess its biological efficacy on hemoglobin (Hb) level and red blood cell (RBC) count in patients with chemotherapy-induced anemia (CIA).

Methods: An open label phase Ib/II trial, monitored by a U.S. CRO (Pharm-Olam International), was conducted in patients developing anemia after chemotherapy treatment. Three cohorts of 6 CIA patients received 8 weeks of treatment with PBI-1402 once a day, at different doses, and were monitored every two weeks for safety, tolerability, Hb level, RBC count and blood chemistry. Patients remained on their chemotherapy during PBI-1402 treatment.

Results: To date, 12 CIA patients have completed their PBI-1402 treatment. 83% of patients demonstrated a significant increase in RBC ($p = 0.015$) and 66% in Hb ($p = 0.038$). Among the responders, the mean Hb increase was 1.1 g/dL ($p = 0.0007$) from a baseline Hb value of 9.8 g/dL. No patient required a blood transfusion and only one patient had an Hb content below 9 g/dL (8.9 g/dL). PBI-1402 was well tolerated and no significant side effects were observed.

Conclusion: PBI-1402, via a mechanism of action distinct from erythropoietin, induced sufficient erythropoiesis to raise the RBC level and Hb in CIA patients. In addition, PBI-1402 is safe and well tolerated. PBI-1402 offers the potential for a novel therapy of the anemia of CIA.

Background

PBI-1402 increases the production of immature progenitors, stem cells, from bone marrow. It also promotes the differentiation of these immature stem cells in CFU-GEMM (Table 1). Furthermore, PBI-1402 promotes the maturation of BFU-E and this effect results in an increase of production of reticulocytes (phase I, human volunteers) and red blood cells (preclinical studies and phase Ib/II CIA clinical trial). An *in vitro* additive proliferation effect is observed in combination with EPO (Figure 1), G-CSF, GM-CSF, IL-3 and SCF. PBI-1402 demonstrates immunorestorative activity of bone marrow and lymphoid organs in immunosuppressed animals. PBI-1402 has antitumor efficacy in animal models.

Anemia is one of the most serious side effects caused by chemotherapy, with bone marrow suppression being the major contributing factor. The treatment with rhEPO is active in only 50-60% of CIA patients. Furthermore, typical doses of rhEPO required to treat CIA patients are two to three fold higher than those used to treat anemia in dialysis patients.

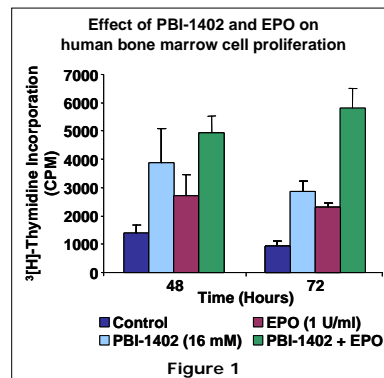
Table 1. Effect PBI-1402 on human bone marrow: *In vitro* colony formation units in myelocult/FBS

	BFU-E	CFU-GM	CFU-GEMM	Total CFC
Control	49	26	2.5	77
PBI-1402 (16 mM)	268	34	4.25	306

Alberta Cancer Research results (repeated by ProMetic and Hôpital Maisonneuve-Rosemont)

Table 1 represents the effect of PBI-1402 on human *in vitro* colony formation units in bone marrow cells. PBI-1402 promotes BFU-E, CFU-GM and CFU-GEMM differentiation. However, a predominant effect on erythroid progenitors was observed in the presence of PBI-1402.

Figure 1 represents the proliferative effect of PBI-1402 and EPO on human bone marrow cells. Both PBI-1402 and EPO induce a significant increase in bone marrow cell proliferation at 48 and 72 hours. Combination of PBI-1402 and EPO resulted in an additive effect on human bone marrow cell proliferation.



Methods

This phase Ib/II trial has been conducted in Eastern Europe under the supervision of Pharm-Olam International Ltd., a U.S.-based clinical research organization. Patients recruited were anemic as a result of chemotherapy and their chemotherapy treatment continued throughout the duration of this trial. **Table 2** summarizes the protocol synopsis. The trial design included three cohorts of six patients at three doses (44, 66 and 88 mg/kg). The end parameters (Hb, RBC and Ht) were compared against each patient's baseline level at entry.

Table 2. Summary of PBI-1402 protocol synopsis.

Primary end point:	Safety and tolerability of PBI-1402.
Secondary end point:	Biological efficacy of PBI-1402 on Hb, RBC and Ht.
Inclusion criteria:	Hb between 90 and 110 g/L, adequate liver and renal function.
Exclusion criteria:	Patients with anemia due to folate and vitamin B12 deficiency, hemolysis, bleeding, or active infection. Patients who have received rhEPO within eight weeks before baseline evaluation, or two+ RBC transfusions (4 weeks), or any RBC transfusion (2 weeks).
Study protocol:	Three cohorts of six CIA patients received eight weeks of oral treatment with PBI-1402 once a day, at three doses (44, 66 and 88 mg/kg). Monitoring every two weeks for Hb level, RBC count, Ht, and monitoring once a month for blood chemistry and adverse events.

Results

To date, 12 CIA patients have completed their eight week oral treatment with PBI-1402. Patients remained on their chemotherapy during treatment. Chemotherapy agents used in patients are taxol, CDDP (cisplatin) 5-FU/leucovorin, mitomycin-C, cyclophosphamide and methotrexate. Only two patients reported side effects to PBI-1402 treatment. These side effects were of low grade.

Table 3 represents the number of adverse events related to PBI-1402 reported by two patients.

Adverse events	Number of episodes
Oesophagitis	2
Dyspepsia	1
GI discomfort	1
Metal taste/Burning sensation	2

Table 5 represents the mean Hb level of PBI-1402-treated CIA patients. Among the responders, the mean Hb increase was 1.2 g/dL ($p = 0.0007$) from a baseline value of 9.8 g/dL.

Baseline	Mean Hb level (g/dL)	p-value
Baseline	9.8	
Responders	11	< 0.0007
All patients	10.5	< 0.038

Table 4 summarizes the results on safety/tolerability and biological efficacy. Eighty-three percent (83%) of patients demonstrated a significant increase in RBC ($p = 0.015$), 66% in Hb ($p = 0.038$) and Ht ($p = 0.001$). No patient required blood transfusion.

Patients	Number	%
Completed the study	12	
Increase in Hb	8	66
Increase in RBC	10	83
Increase in Ht	8	66
Requiring transfusion	0	0

Table 6 summarizes the Hb level of all patients after treatment. Seventy-five percent (75%) of CIA patients achieved Hb level greater than 10 g/dL, 50% greater than 10.5 g/dL and finally 33% greater than 11 g/dL. No patient required a blood transfusion and only one patient had an Hb level below 9 (8.9 g/dL).

Hb level (g/dL) after treatment	% of patients
> 10	75
> 10.5	50
> 11	33
< 9 (8.9)	8

Figure 2 represents the effect of oral treatment of PBI-1402 on hematocrit level in responders (8 patients) versus non-responders (4 patients). PBI-1402 induces a significant increase in hematocrit level from week 2 to week 8 in responders. PBI-1402 stabilizes the hematocrit level in non-responders.

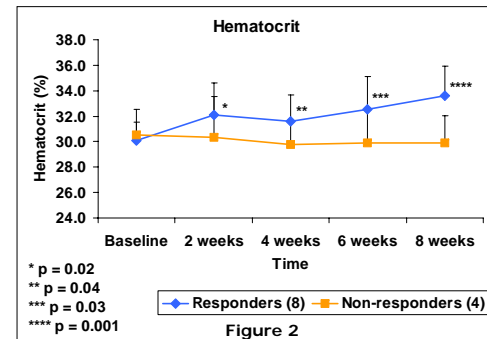


Figure 3 represents the effect of oral treatment of PBI-1402 on RBC in responders (10 patients) versus non-responders (2 patients). PBI-1402 induces a significant increase in RBC from week 2 to week 8 in responders. PBI-1402 stabilizes RBC count in non-responders.

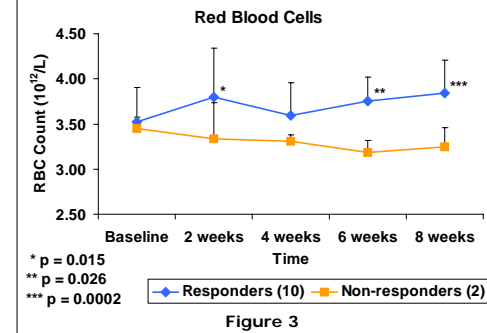
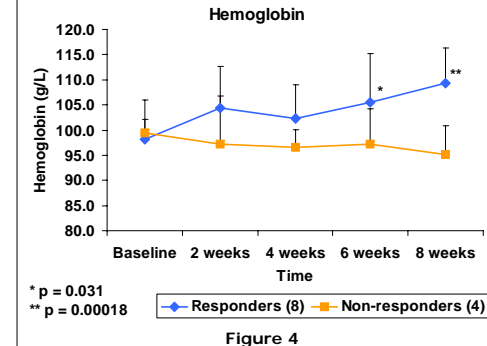


Figure 4 represents the effect of oral treatment of PBI-1402 on Hb level in responders (8 patients) versus non-responders (4 patients). PBI-1402 induces a significant increase in Hb level from week 6 to week 8 in responders. PBI-1402 stabilizes Hb level in non-responders.



Conclusion

PBI-1402 offers the potential for a novel therapy of anemia.

PBI-1402 strengths:

- 1) **Safe:** Clinical phase I: 50 healthy individuals; Clinical phase Ib/II: 12 CIA patients
- 2) **Oral activity:** Increase of RBC, Ht and Hb levels in CIA patients
- 3) **Distinct mechanism of action:** Additive effect in combination with rhEPO
- 4) **Reduced cost**

There are no relevant conflicts of interest to disclose.