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Efficacy and Safety of ior® EPOCIM for Chemotherapy- or Radiotherapy-Induced Anemia in Pediatric Cancer Patients


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Oakland, Estados Unidos

Available in: http://www.redalyc.org/articulo.oa?id=437542103007
Efficacy and Safety of ior®EPOCIM for Chemotherapy- or Radiotherapy-Induced Anemia in Pediatric Cancer Patients

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ABSTRACT
INTRODUCTION: Recombinant human erythropoietin (RHuEPO) is an erythropoiesis stimulating agent (ESA) used to treat anemia in patients with total or relative erythropoietin deficit. In cancer patients, it is administered to optimize hemoglobin (Hb) levels, correct anemia and reduce the need for transfusions. Cuba produces a RHuEPO, registered in 1998 as ior®EPOCIM, that is widely used in the national public health system, mainly to treat patients with anemia due to chronic kidney disease (CKD).

OBJECTIVE: Evaluate the efficacy and safety of ior®EPOCIM in pediatric cancer patients with anemia following chemotherapy or radiotherapy. The working hypothesis posed an Hb increase ≥15 g/l in 70% of patients receiving ior®EPOCIM for 8 weeks.

METHODS: A Phase IV, multicenter, open clinical trial was conducted. Participants were 157 patients aged 1–19 years with anemia and cyto-histological diagnosis of cancer in any location. Patients received either 800 U/kg ior®EPOCIM intravenously, once weekly, or 150 U/kg ior®EPOCIM subcutaneously, 3 times a week, for 8 weeks. All patients had blood tests every week to determine hemoglobin and hematocrit, and reticulocyte and platelet counts. Mean number of transfusions required by patients during the treatment period was compared to the mean number of transfusions received in the preceding 8 weeks. Adverse events (AE) were recorded at the 4th and 8th weeks and classified by intensity and causality.

RESULTS: Hb levels rose ≥15 g/l in 68.8% of patients, and transfusion requirements decreased 17%. The most frequent adverse events were fever (19.3%), vomiting (10.2%) and flu-like syndrome (9.6%). Intensity of AE was predominantly mild. Only 7 AE were classified as very probably related to the product and none of those was severe.

CONCLUSIONS: ior®EPOCIM proved to be safe and effective at the doses and frequencies used in this patient population. As a result, this medication was recommended for use in all pediatric oncology and hematology services in the country.

Keywords: Erythropoietin, recombinant; anemia, cancer, pediatrics, medical oncology, Cuba

INTRODUCTION
Erythropoietin (EPO), a glycoprotein manufactured mainly in the kidney, is the major factor regulating production of red blood cells and is essential for their proliferation, differentiation and maturation in bone marrow.[1,2] Discovery of the human EPO gene in 1985 enabled development and production of recombinant erythropoietin (RHuEPO) for clinical use, transforming anemia treatment, particularly for patients with end-stage renal disease.[3–5] Several clinical studies of dialysis patients receiving RHuEPO showed erythropoiesis stimulation and correction of renal anemia, fewer transfusions and, as a result, improved quality of life.[6–8]

RHuEPO products, including epoetin alpha (Eprex® Epogen®, Procrit®), epoetin beta (NeoRecormon®), darbepoetin alpha (Aranesp) and CERA (Continuous Erythropoietin Receptor Activator) are currently classified and marketed internationally as erythropoiesis stimulating agents (ESA).[9] ESAs have been used effectively to treat anemia associated with a variety of conditions, most frequently chronic kidney disease (CKD), prematurity, and HIV infection. They are also used to increase Hb levels during surgery; following radiotherapy, chemotherapy or transplant; in situations when red blood cell transfusion is ruled out; or to improve autologous transfusion response.[10]

In Cuba, however, patients with anemia due to CKD were unable to benefit from RHuEPO treatment due to the high price of ESAs in the international market. The Molecular Immunology Center (CIM, its acronym in Spanish) therefore began RHuEPO research and development, obtaining a product registered as ior®EPOCIM in 1998 by the national drug regulatory agency CECMED (its ac-
between adults and children.[17] The French Cancer Institute’s Recommendations for Erythropoiesis Stimulating Agents in the Management of Anemia in Children with Cancer indicate that the decision to treat with ESAs should be made case by case, and caution against systematic administration of ESAs for a prolonged period, while noting there does not seem to be association between ESA use as indicated and significant toxicity in children.[18]

In Cuba in 2008, a Phase IV clinical trial was conducted to assess the efficacy and safety of ior®EPOCIM treatment for anemia in 338 adult patients with radiotherapy- or chemotherapy-induced anemia. Patients received 10,000 U ior®EPOCIM subcutaneously, 3 times a week for 8 weeks. Results showed a 21.7 g/l increase in mean Hb level and a 31.4% reduction in transfusions at conclusion of the study. The most frequent adverse events were pain at the injection site and bone pain: 23.5% and 13.8%, respectively, of total events reported.[25]

Considering the results of that clinical trial, as well as a literature review of studies treating pediatric patients with RHuEPO, and the current international guidelines mentioned above, a clinical trial was conducted to assess the efficacy and safety of ior®EPOCIM in pediatric cancer patients with radiotherapy- or chemotherapy-induced anemia. The working hypothesis posed an Hb increase ≥15 g/l in 70% of patients receiving ior®EPOCIM for 8 weeks.

METHODS

Study Design An open Phase IV non-controlled, multicenter clinical trial was conducted. The study universe was comprised of 157 pediatric cancer patients who fulfilled inclusion criteria and were treated between September 2004 and August 2006 in the oncology or hematology departments of 8 participating hospitals in Cuba.

Inclusion criteria Patients aged 1–19 years with cyto-histological diagnosis of cancer in any location and anemia clinically associated with chemotherapy or radiotherapy, not previously treated with RHuEPO. Anemia was defined as Hb ≤110 g/l for patients aged 1–11 years and Hb ≤120 g/l for patients aged 12–19 years.[26]

Prior to inclusion in the study, written informed consent was obtained from a parent or guardian of each patient, signed in the presence of the clinical investigator in the participating institution and a witness.

Exclusion criteria Known hypersensitivity to products derived from higher cells or human albumin, active hemorrhage or hemolysis, or uncontrolled high blood pressure at time of inclusion.

Suspension criteria Hb ≥140–150 g/l achieved prior to week 8 of treatment; appearance of an exclusion criterion; adverse event implying risk to the patient, at the discretion of the clinical investigator; patient’s death.

Ethical Considerations The research protocol was approved by the Clinical Research Ethics Committees of the participating institutions. The national drug regulatory agency, CECMED, was notified as required for Phase IV clinical trials of a registered product. Helsinki Declaration criteria,[27] International Ethical Guidelines for Biomedical Research involving Human Subjects,[28] and Standard Working Procedures of the National Coordinating Center of Clinical Trials (CENCEC, its acronym in Spanish)[29] were followed.

Treatment Patients received either 600 U/kg ior®EPOCIM intravenously, once a week, or 150 U/kg ior®EPOCIM subcutaneously in the right deltoid muscle, 3 times a week, for 8 weeks, consistent with International Guidelines for the use of Erythropoiesis Stimulating Agents.[17] Administration route was assigned by the clinical investigator, according to the patient’s chemotherapy schedule. The intravenous route was used in 81 patients, and the subcutaneous route in 76 patients. Dosage for each patient was calculated by the clinical investigator, based on patient’s weight and administration route. Patients were hospitalized or ambulatory during treatment, at the discretion of the clinical investigator, taking into account each patient’s clinical status.

Hb levels were measured weekly, as well as hematocrit, and reticulocyte and platelet counts. Patients whose Hb dropped below initial levels were given transfusions, at the discretion of the clinical investigator, and continued ior®EPOCIM treatment.

Hb levels were evaluated at the conclusion of week 4 of treatment, and the ior®EPOCIM dose was maintained in patients whose Hb had risen ≥10 g/l above initial values. In patients whose Hb had not increased ≥10 g/l above initial values, the intravenous dose was increased to 900 U/kg weekly, and the subcutaneous dose to 300 U/kg three times a week.

Data collection and analysis A data collection logbook was kept for each patient, completed by the clinical investigator in each participating institution. The patient’s clinical evolution was recorded weekly during the 8-week study period, as well as weight, ior®EPOCIM dose, and lab test results (hemoglobin, hematocrit, reticulocyte and platelet count at treatment onset and termination, serum iron levels and transferrin saturation index).

Efficacy was measured against the study hypothesis and transfusions required during the study compared to the number of transfusions in the 8 weeks prior to inclusion in the study.

Hb response during ior®EPOCIM treatment was evaluated by calculating the difference between initial and final mean Hb levels.

Safety was measured by registry and analysis of adverse events (AE), defined as any harmful clinical event in a patient receiving the product under study, not necessarily implying a causal relationship with the treatment. AEs were recorded cumulatively by the clinical investigator at the conclusion of week 4 and week 8.

Adverse events were classified by intensity and causality according to CENCEC’s Standard Working Procedure for registering adverse events.[29] The Jones algorithm was also used to classify causality.[30] Intensity was classified as mild, moderate, less severe, or severe; and causality was classified very probable, probable, possible, or remote. In accordance with CENCEC’s procedures, only those AE classified Very Probable were considered associated with use of the medication.[29]

Data analysis was performed by “protocol” (only data from patients completing treatment) and by “intent to treat” (data from all patients initially included in the study). Databases were created
RESULTS

Of 157 patients initially included in the study, 129 completed treatment and 125 were included in the data analysis. After 8 weeks of ior®EPOCIM treatment, 68.8% of patients (86/125) attained an Hb increase ≥15 g/l, and 59.2% (74/125) attained an Hb increase ≥20 g/l (Table 1). In the intent-to-treat analysis, 54.8% of patients (86/157) attained an Hb increase ≥15 g/l, and mean Hb rose 20.94 g/l, from 90.14 g/l at study onset to 111.08 g/l at termination.

Table 1: Hemoglobin Increase at Week 8 of ior®EPOCIM Treatment

<table>
<thead>
<tr>
<th>Hemoglobin Increase</th>
<th>≥15 g/l</th>
<th>≥20 g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
<td>68.8</td>
</tr>
<tr>
<td>No</td>
<td>39</td>
<td>31.2</td>
</tr>
<tr>
<td>Total Patients</td>
<td>125</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2: Patient Characteristics and ior®EPOCIM Administration Routes

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Administration Route</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td>No. %</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Skin Color</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td>Mixed Race</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Solid Tumor</td>
</tr>
<tr>
<td></td>
<td>Hematological Malignancy</td>
</tr>
<tr>
<td>Total Patients (n=125)</td>
<td></td>
</tr>
</tbody>
</table>

Expected response (Hb increase ≥15 g/l) at 8 weeks was significantly greater in patients receiving ior®EPOCIM subcutaneously (78.2%) compared to those treated intravenously (61.4%) (Table 3). During the study, the number of patients requiring transfusions declined 15.3%, and the number of transfusions decreased 17.1%. In the 8 weeks preceding onset of ior®EPOCIM treatment, 91 patients (58.0% of study universe) received a total of 181 transfusions, compared to 67 patients (42.7% of study universe) requiring a total of 150 transfusions during treatment.

In the causality analysis only 7 AE (4.2%) were classified as having a very probable association with exposure to ior®EPOCIM, none of these severe; 2 fever events were considered mild; 1 bone pain, 1 redness, and 1 vomiting, all moderate; 1 burning sensation and 1 pain at injection site were classified as less severe. Remaining AE were classified as Probable (5.5%), Possible (65.5%) and Remote (24.8%) (Table 5).

DISCUSSION

The 68.8% response in the present study was considered clinically acceptable, even though below the 70.0% posed in the working hypothesis. It also falls within the 46%–75% response range for mean Hb increases ≥ 2 g/dl (20 g/l) at 8 and 12 weeks of treatment, reported in international studies using epoetin alpha to treat pediatric cancer patients with anemia.[20,22–24]

In a study at St. Jude Children’s Research Hospital in the United States, 217 patients aged 5–18 years were randomized to receive 600 U/kg of epoetin alpha intravenously or placebo. On day 29, a 2 g/dl (20 g/l) Hb increase was attained in 56.5% of the epoetin-treated group and 34.9% of the placebo group.[31] Researchers in Greece reported a 2 g/l Hb increase at 8 weeks in 46% of 50 patients with hematologic malignancies and solid tumors, treated with 150 U/kg, 3 times a week.[24] A higher
response was obtained in a study conducted in Spain to evaluate erythropoietin alpha in 25 patients with different types of solid tumors. They received 150 U/kg of erythropoietin alpha, 3 times a week, for 3 months and attained a 2 g/dl (20 g/l) Hb increase in 75% of patients.[23]

In a study carried out in Turkey, 34 children aged 1–16 years with solid tumors were randomized to receive 150 U/kg of erythropoietin alpha or placebo, 3 times a week, for 8 weeks. A significant decrease in the number of patients requiring transfusions and a 20 g/l increase in mean Hb were obtained in the treated group, while there was no change in the control group.[21]

According to these and other published studies, RHuEPO is safe and well-tolerated as used to correct anemia in pediatric cancer patients. None of the most frequent adverse events reported in the present study were mentioned in any of the studies reviewed, and those AE reported were mostly transient, local reactions, such as redness and burning sensation. [21–24,31–33]

Although weight loss was the fourth most frequent AE reported in the present study, it was considered associated with patients’ primary disease and not with treatment, as other authors have explained.[34,35]

In the present study, a better response was achieved with subcutaneous administration of ior®EPOCIM than with intravenous administration. Similar results have been reported in adult hemodialysis patients with anemia,[36,37] but we found no other studies comparing response by administration route of RHuEPO in children or adults with cancer. A limitation of the present study was lack of an established, uniform, criteria for assigning administration route, which was left to the discretion of the clinical investigator, based on patients’ chemotherapy schedules and hospitalization conditions in each institution. Further research is needed to develop evidence-based criteria for assigning administration route, and to compare and analyze response to RHuEPO treatment by administration route in pediatric cancer patients.

This study is the first clinical trial using Cuban recombinant human erythropoietin (ior®EPOCIM) to treat anemia in pediatric cancer patients, thereby providing baseline data for future research. It is also contributes to the literature in an area on which few studies have been published internationally. The study was particularly important in Cuba, from a clinical standpoint, as it gave Cuban oncologists and hematologists—especially those in pediatrics—an opportunity to gain new experience in the use of ior®EPOCIM.

Based on the results obtained, introduction of ior®EPOCIM in all pediatric oncology and hematology services in the country was recommended.

CONCLUSIONS
The Cuban ESA, ior®EPOCIM, proved effective in correcting anemia and reducing transfusion requirements in pediatric cancer patients. It also proved to be safe and well-tolerated, as evidenced by the low frequency of adverse events associated with treatment.

ACKNOWLEDGMENTS
We gratefully acknowledge the collaboration of all the researchers who participated in the patient inclusion phase of the study and assisted in data collection. Without them, completion of the study would not have been possible.

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Submitted: October 26, 2009
Approved for publication: June 25, 2010
Disclosures: None