Transfusion Medicine

Erythrocytapheresis plus erythropoietin: an alternative therapy for selected patients with hemochromatosis and severe organ damage

We report the efficacy, tolerability and cost of erythocytoapheresis plus recombinant human erythropoietin (rHuEPO) in three patients with severe hereditary hemochromatosis (HH). Results indicate that this regimen could be a valid therapeutic alternative in complicated HH patients. Its cost, however, limits its use to patients whose clinical conditions prevent a proper phlebotomy regimen.

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Erythrocytapheresis (EA) is effective in removing iron excess in patients with hereditary hemochromatosis (HH),[1-3] but there are no established criteria for its use in HH.[4] We report the efficacy, tolerability and cost of EA in three C282Y homozygous patients with advanced HH. The first patient developed atrial flutter at the age of 57 years that required surgical ablation which was complicated by septic endocarditis and mitral insufficiency. The second patient, aged 64, suffers from chronic bronchitis with chronic respiratory failure. Both these patients underwent liver biopsy that showed cirrhosis and severe iron overload. The third patient was a drug-addict and heavy drinker until he was 20 years old. Subsequently he underwent splenectomy for traumatic rupture and developed hypogonadism and diabetes. At the age of 39 he was admitted for acute heart failure: echocardiography showed hypokinetic cardiomyopathy (ejection fraction: 35%). Clinical and biochemical data indicated marked iron overload and hepatic cirrhosis, but liver biopsy was not performed because of the severe heart disease. All three patients were referred to us for counselling since they were unable to tolerate phlebotomy (dizziness and faintness during and soon after venesection, and fatigue). Patient 3 was on desferrioxamine treatment that was stopped when he started EA.

EA was performed using a computer-guided continuous flow cell separator in each patient (Spectra, COBE BCT, Lakewood, CO, USA). Pre-EA hematocrit was higher than 40%. For the patients' safety, procedure parameters were set to achieve a final hematocrit not lower than 30% (mean 34%; range 30.9-36.8%). Recombinant human erythropoietin (rHuEPO) was administered at the dosage of 10000 UI/week (about 150 UI/kg/week); this was reduced to 5000 UI/week in patient 1 because he developed a very high pre-EA hematocrit value, complained of headache and showed conjunctival hemorrhage. EA was well-tolerated in all patients and no procedure-related side effects were observed. Patients 1 and 2 achieved iron depletion. Table 1 summarizes the results.

Standard treatment in HH patients consists in weekly phlebotomy until iron depletion,[5] but in our patients this was not feasible because of the adverse effects related to the procedure itself and the patients' clinical status. All 3 patients experienced symptoms related to hypovolemia which were not significantly relieved even by reducing the amount of blood removed to below 400 mL (the volume we usually remove in individuals of normal weight). Decreasing the frequency would have further decreased the efficacy of the therapy and excessively prolonged the time of exposure to iron toxicity. Daily subcutaneous infusion of desferrioxamine is an alternative therapy to phlebotomy in HH patients who do not tolerate venesections,[4] but iron chelation alone is less efficient than phlebotomy. Furthermore, in our experience, in adult HH patients compliance to treatment decreases after a few months.

Taking into account the severity of the clinical status and iron overload of these 3 patients we planned a cautious EA program in combination with rHuEPO and demonstrated that this regimen is feasible and efficient. A further benefit of EA is that it spares plasma proteins, platelets and clotting factors[1,6] (especially useful in patients with cirrhosis). The amount of iron removed by EA was similar to that removed by a weekly phlebotomy (400 mL) regimen. To compare the efficacy of EA vs phlebotomy we corrected the amount of blood we could remove at each venesection for the patient's baseline hematocrit to obtain the amount of packed red blood cells (RBC) and iron removed (1 mL RBC = 1 mg iron), and normalized the amount of packed RBC removed at each EA to a 4-week period. We estimated that the amount of iron removed by EA was equivalent to 3.4, 4.7 and 4.5 phlebotomies in the three patients. Faster iron depletion has been previously reported by using a very intensive EA regimen (pre-EA hematocrit of 34%) but, in our opinion, this regimen is hard to propose as standard therapy.[1] In patients #2 and 3 we evaluated a mean daily increase of 0.16 g/dL of hemoglobin after EA and, based on this, we established that a standard interval of about

Table 1. Main data at baseline, during and after erythrocytapheresis (EA). The table also reports data regarding the EA procedure and the amount of iron removed.

	Patient #1	*Patient #2*	*Patient #3*
Age (years)	58	64	40
Transferrin sat. (%) baseline→last	93→41	78→37	>100→96
Serum ferritin (μg/L) *baseline → last*	1794→67	4954→82	7093→606
Alanine transferase (IU/L) *baseline → last*	56→16	79→31	51→23
Number of EA	15	22	15
Interval between EA (days)	30	25	26
Hematocrit pre EA (%) (mean±SD)	45.8±3.1	46.6±0.6	48±2.4
Hematocrit post EA (%) (mean±SD)	33.6±1.9	33.5±0.1	35±1.4
Iron removed/EA (mg) (mean±SD)	590±111	715±135	617±139
Iron removed (g)	8.84	15.72	9.26

Total iron removed was calculated by the amount of packed red cells collected (1 mL of packed red cells = 1 mg of iron). The amount of packed red cells removed was calculated by the amount of blood removed corrected for the hematocrit value. Patient 3 is still on EA treatment. Total iron removed by desferrioxamine before EA was about 3 g.

25 days was sufficient for safe and efficient EA. Compared to phlebotomy, EA is more complex and requires adequate equipment and trained staff. Furthermore, based on regional figures, we estimated a cost of 602€ for each EA, whereas the cost for each phlebotomy is 35€. Adding the price of rHuEpo (5000 U = 91.62€), the total estimated cost of treatment was 15286€, 27152€, and 11876€ for patients #1, 2 and 3, respectively. By contrast, the cost of standard phlebotomy therapy would have been approximately 1925€, 3430€ and 1400€, respectively, 8 times less expensive than EA. For this reason we suggest that EA should only be proposed for selected HH patients with major iron overload whose clinical conditions prevent the execution of a proper phlebotomy regimen (regular frequency and adequate amount of blood removed).

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