Similar favorable outcome of pegfilgrastim overdose in patients with different age and underlying disease

Although pegfilgrastim is increasingly used in children and adults[1-4] no reports are found on over-dosage. We present the outcome of 2 patients aged two and 79 years who by mistake received a remarkable overdose of pegfilgrastim. Patient #1 was a 2-year old boy, with severe congenital neutropenia (ELA 2 mutation g.1894T>C L30P; exon 2) whose outcome is detailed elsewhere.[4] While on pegfilgrastim 100 μg/kg, during a febrile episode, he received by mistake a pegfilgrastim overdose of 937 μg/kg (6 mg) instead of the scheduled 100 μg/kg, as the nurse in charge confused the vial of pegfilgrastim with that of filgrastim and inadvertently gave the entire vial to the patient. The administration of an entire vial did not arouse suspicion as it would have corresponded to 20 μg/kg of filgrastim, still a practicable dose in SCN patients. The patient's parents were immediately informed of this error and of possible complications. Incident reporting procedures were activated according to the policy of our Institute. No data were traceable in literature and also an Italian branch of the manufacturing company (Amgen) did not possess information on such a high overdose in children. Tight clinical, respiratory and laboratory monitoring was promptly established. The child remained well with no respiratory symptoms, O_2 saturation of 98-100% without supportive respiratory measures and the fever disappeared in two days. Hb and platelets remained above 11 g/dL and 250×10⁹/L. Renal and liver function tests and serum electrolytes stayed within normal ranges. Chest X-ray showed only a minimal interstitial overload. No hepatosplenomegaly was demonstrable on repeated ultrasound scans. WBC, ANC and pegfilgrastim serum level are shown in Figure 1.

On d+11 the patient was discharged with no toxicities, a WBC of 25.4×10⁹/L, ANC of 4.31×10⁹/L and given daily filgrastim. Two years later, due to poor infection control and "possible" fungal pneumonia, he was again put on pegfilgrastim (100 μg/kg every 12 days) on which he is still well 45 months after overdose. There have been no further hospitalizations for infections. WBC are 9.8×10⁹/L, ANC 3.23×10⁹/L (d+3 from pegfilgrastim), Hb 9.2 g/dL, platelets 374×10⁹/L. Neither dysplastic cells nor cytogenetic clone have been found in the marrow.

Patient # 2 is a 79-year old male with Sézary syndrome treated with mini CEOP.[5] Nine days after the first course, on routine examination, he revealed he had self-administered one injection/day of pegfilgrastim from d+1 to d+8, (48 mg=800 μg/kg) instead of 6 mg on d+1 only (100 mcg/kg) as prescribed. The patient was asymptomatic and physical examination was normal with no splenomegaly. After consultation with the Colleagues who had experienced the uneventful outcome in patient 1, he was discharged with indication of a three times/week clinical and biochemical monitoring. WBC, ANC and pegfilgrastim serum levels are shown in Figure 2. Grade 2 bone pain responded to oral paracetamol. On d+15 he was hospitalized due to dyspnea and bilateral leg swelling. Arterial oxygen saturation was 94%, pH 7.52, pO_2 45.8 mmHg, pCO_2 32.4 mmHg, HCO_3-27.6 mmol/L. Chest CT scan excluded pulmonary embolism and disease progression, and showed reduction of known lymphoadenopathies, moderate emphysema and bilateral pleural effusion of 15-20 mm diameter. No hepatosplenomegaly was detected. Hb dropped to 7.1 g/dL requiring a unit of packed red cells; platelets declined to 51×10⁹/L and then gradually normalized. The patient was successfully treated with oxygen mask therapy, furosemid and prednisone (0.5 mg/kg), and when WBC and ANC normalized (d+20) he was discharged. After a full recovery, two further mini-CEOP courses were administered without pegfilgrastim. ANC normalized after both cycles. Unfortunately, despite normal ANC, *Staphylococcus aureus* meningitis occurred 63 days after the third mini CEOP and the patient died, three months after pegfilgrastim overdose.

This is the first report on the pharmacokinetics and clinical effects of pegfilgrastim overdose in pediatric and adult patients. Patient # 1, even with a dose 9.37-fold greater than scheduled, did not experience either organ or biochemical toxicities. While recognizing the gravity of the original mistake, it is important to note that the availability of pediatric formulations might help reduce the occurrence of these errors.

Patient # 2, who received an 8-fold higher dose than prescribed, also had no biochemical and organ toxicity apart from a respiratory distress requiring hospitalization which was reverted by standard treatment in seven days. Pleural effusion seemed to be attributable to the overdose as it coincided with ANC peak (101×10⁹/L). A high num-

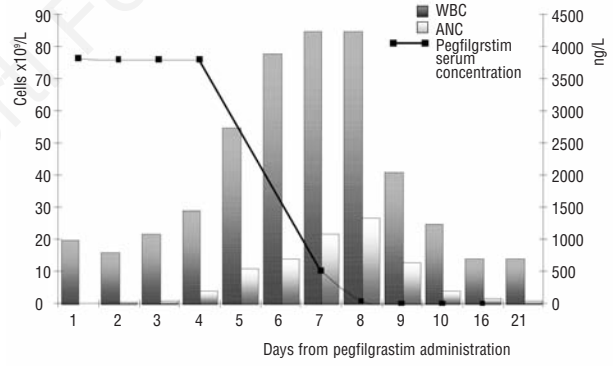

Figure 1. WBC, ANC and pegfilgrastim serum level after overdose in patient 1. Outcome of WBC and ANC in patient 1 after the injection of a pegfilgrastim overdose 9.37-fold greater than scheduled. Pegfilgrastim serum concentration is shown on the right y-axis.

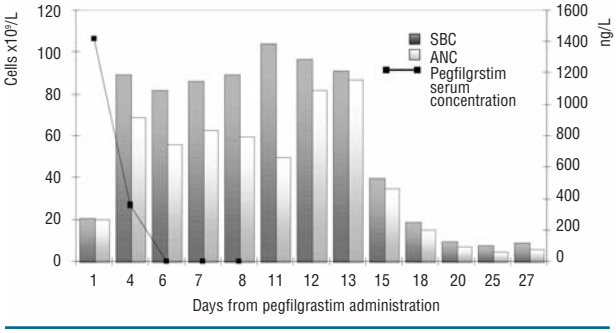

Figure 2. WBC, ANC and pegfilgrastim serum level after overdose in patient 2. Outcome of WBC and ANC in patient 2 after the injection of a pegfilgrastim overdose 8-fold greater than prescribed. Pegfilgrastim serum concentration is shown on the right y-axis.

ber of activated neutrophils may have altered local vessel permeability[6,7] although the possibility that chemotherapy may have contributed to this cannot be excluded. Overdose probably had no adverse affect on the outcome of the underlying disease as shown by a reduction of lymphnodes on CT scan. Meningitis, occurring three months after the overdose, was more likely due to steroid-induced immunosuppression with comorbidities (age, hypertension, emphysema) contributing to its lethal outcome. A role for pegfilgrastim cannot be fully excluded but, since it was undetectable in the serum on day +6 and recovery of ANC after subsequent courses was as expected, its role would seem to be negligible.

Recently the death of a patient with GSDIb was reported after 120 μg/kg of pegfilgrastim that were considered contributory to this event as aggravating pre-existing pulmonary arterial hypertension (PAH).[8] Different outcomes can be explained by the worse comorbidities (recurrent enteritis, total colectomy, interstitial nephropathy, PAH, liver adenomas, recent respiratory infection) of the GSDIb patient compared to our patient # 2.

WBC kinetics were similar in our patients, normalizing in both after d+20, whereas ANC peak was lower in patient # 1 as a consequence of the underlying disease. Hemoglobin and platelets were unaffected in patient # 1 whereas these dropped in patient # 2, more likely as an effect of chemotherapy rather than of pegfilgrastim. Serum drug levels peaked on d+1 in both patients and returned to baseline later in patient # 1 (d+16) *vs.* patient # 2 (d+6) in accordance with neutrophil-mediated kinetics of pegfilgrastim[9,10] by which patient # 2, whose neutrophil circulatory output was far greater than in patient # 1 (peak of 101×10^9/L *vs.* 20×10^9/L), cleared the drug more rapidly from the bloodstream.

Data on drug overdoses in humans are extremely rare to find. This report provides useful information to physicians indicating that overdose in children may have an uneventful outcome and in elderly patients may produce controllable side effects.

Carlo Dufour,[1] Barbara Cappelli,[2] Michaela Calvillo,[1] Francesca Fioredda,[1] Rossella Tonelli,[3] and Roberto Crocchiolo[4]

[1]Hematology Unit, G.Gaslini Children's Hospital, Genova, Italy;[2]Pediatric Immunohematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milano, Italy;[3]Mario Negri Institute for Pharmacology, Milano, Italy;[4]Unit of Lymphoid Malignancies, San Raffaele Scientific Institute, Milano, Italy.

Key words: neutropenia, pegfilgrastim, overdose, pharmacokinetic.

Acknowledgments: Fondazione Compagnia di San Paolo and ERG s.p.a, are acknowledged for supporting the activity of the Hematology Unit of G.Gaslini Children's Hospital.

Correspondence: Carlo Dufour, MD, Head Hematology Unit, G.Gaslini Children's Hospital, Largo G.Gaslini 5, 16147 Genova, Italy. Phone: 0039 01 56 36 694; Fax: 0039 010 56 36 714. E-mail: carlodufour@ospedale-gaslini.ge.it

Citation: Dufour C, Cappelli B, Calvillo M, Fioredda F, Tonelli R. Similar favorable outcome of pegfilgrastim overdose in patients with different age and underlying disease. Haematologica. 2010;95:684-685. doi:10.3324/haematol.2009.018333

References

1. Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon P, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol. 2003;14(1):29-35.
2. Bruns I, Steidl U, Fischer JC, Czibere A, Kobbe G, Raschke S, et al. Pegylated granulocyte colony-stimulating factor mobilizes CD34+ cells with different stem and progenitor subsets and distinct functional properties in comparison with unconjugated granulocyte colony-stimulating factor. Haematologica. 2008; 93(3):347-55.
3. Beaupain B, Leblanc T, Reman O, Hermine O, Vannier JP, Suarez F, et al. French SCN Registry, Service d'Hémato Oncologie Pédiatrique. Is pegfilgrastim safe and effective in congenital neutropenia? An analysis of the French Severe Chronic Neutropenia registry. Pediatr Blood Cancer. 2009;53(6):1068-73.
4. Fioredda F, Calvillo M, Lanciotti M, Lanza T, Giunti L, Castagnola E, et al. Pegfilgrastim in children with Severe Congenital Neutropenia. Pediatr Blood Cancer. In press 2009.
5. Merli F, Bertini M, Luminari S, Mozzana R, Botto B, Liberati AM, et al. Long term results of a randomized study performed by Intergruppo Italiano Linfomi comparing Mini-CEOP vs P-VEBEC in elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma. 2007;48(2):367-73.
6. Spiekermann K, Roesler J, Emmendoerffer A, Elsner J, Welte K. Functional features of neutrophils induced by GCSF and GM-CSF treatment: differential effects and clinical implications. Leukemia. 1997;11(4):466-78.
7. Schilero GJ, Oropello J, Benjamin E. Impairment in gas exchange after granulocyte colony stimulating factor (GCSF) in a patient with the adult respiratory distress syndrome. Chest. 1995;107(1):276-8.
8. Donadieu J, Beaupain B, Rety-Jacob F, Nove-Josserand R. Respiratory distress and sudden death of a patient with GSDIb chronic neutropenia: possible role of pegfilgrastim. Haematologica. 2009;94(8):1175-7.
9 Yang BB, Kido A, Shibata A. Serum pegfilgrastim concentrations during recovery of absolute neutrophil count in patients with cancer receiving pegfilgrastim after chemotherapy. Pharmacotherapy. 2007;27(10):1387-93.
10. Holmes FA, Jones SE, O'Shaughnessy J, Vukelja S, George T, Savin M, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Ann Oncol. 2002;13(6):903-9.

Homozygous deletion of *HFE* is the common cause of hemochromatosis in Sardinia

We recently characterized an *Alu*-mediated recombination causing the loss of the complete *HFE* gene sequence. Here, we describe the case of a novel homozygous patient. We further show that *HFE* deletion results from a founder effect and that it represents the common cause of hemochromatosis in Sardinia.

We recently reported the case of a 47-year old woman with a moderate iron overload due to an *Alu*-mediated recombination causing the loss of the complete *HFE* gene sequence.[1] The same chromosomal alteration was identified by Pelucchi and co-workers in another woman. Despite a younger age at diagnosis (29 years), their patient showed a more impressive iron overload.[2]

A third case, a man, came to our attention. At the age of 44 he showed a transferrin saturation level of 80% and a serum ferritin level of 2080 μg/L. He was not genotyped for the p.C282Y and p.H63D variations because of an inability to amplify the *HFE* exons 2 and 4. We confirmed absence of the *HFE* gene in this patient but we were also interested in its origins. Indeed, the patient and both previously reported women were of Sardinian descent.

The Sardinian population is genetically differentiated from the other Caucasian populations.[3] It represents a genetic isolate where the p.C282Y mutation is considered as rare or even absent.[4] This led us to assume that the *HFE* deleted allele was present at the population level and, related to a founder effect, was the common cause of hemochromatosis in this Mediterranean island.

To characterize the contribution of the *HFE* deletion in the Sardinian population, we first established the frequency of this mutation in a sample set of 198 controls