

Successful use of palifermin following severe anaphylaxis to pegaspargase in a pediatric patient with acute lymphoblastic leukemia

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Abstract

Palifermin and pegaspargase are *Escherichia coli*-derived drug products. Hypersensitivity reactions, including anaphylaxis, are frequently reported with pegaspargase. In high-risk acute lymphoblastic leukemia (ALL), patients undergoing allogeneic hematopoietic stem cell transplant may be treated with palifermin as a supportive care measure for mucositis prophylaxis. However, no literature exists documenting the cross-reactivity between palifermin and pegaspargase. We report a case in which a child with very high-risk ALL having experienced severe anaphylaxis with pegaspargase was later successfully treated with palifermin during stem cell transplant conditioning.

Keywords

Pediatric oncology, palifermin, pegaspargase, cross-reactivity, hypersensitivity

Introduction

Palifermin, a recombinant human keratinocyte growth factor (KGF), is produced within an *Escherichia coli* (*E. coli*) vector system. Palifermin is approved for reduction in incidence and duration of severe oral mucositis in adult patients undergoing autologous hematopoietic stem cell transplant (HSCT).¹ Though not approved, a phase I study has demonstrated tolerability in pediatric patients undergoing allogeneic HSCT.² Hypersensitivity reactions (HSRs) are commonly documented with *E. coli*-derived proteins and enzymes.^{3,4} Palifermin is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins.⁵ The true incidence of HSRs to palifermin is largely unknown; however, case reports of skin rashes have been documented since drug approval.^{6–8}

Pegaspargase, an *E. coli*-derived enzyme, is a core component of therapy for pediatric acute lymphoblastic leukemia (ALL). High-risk ALL patients that proceed to allogeneic HSCT may benefit from palifermin. HSRs can occur in patients treated with pegaspargase, with reactions ranging from grade 1 hypersensitivity (e.g., urticaria, erythema) to grade 4 (e.g., hypoxia, loss of

consciousness) and often may follow the second dose.^{3,9} Currently, no data exist within the literature or post-marketing surveillance on the occurrence or rate of cross-reactivity between palifermin and pegaspargase. Our case reports a child with ALL who experienced a severe HSR to pegaspargase, who was later treated with palifermin without allergic reaction.

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Case report

The patient is a 5-year-old boy with very high-risk ALL with no significant medical history nor drug or food allergies who was treated per protocol with Chldren's Oncology Group AALL1131. His day 15 consolidation chemotherapy (pegaspargase, vincristine, and intrathecal methotrexate) was complicated by severe anaphylaxis to his second dose of pegaspargase (2500 units/m²). Of note, the patient did not receive any pre-medications prior to the pegaspargase dose. Symptoms presented 10 min into the 1 h infusion and included laryngospasm, hypoxia, hypotension, bradycardia, and loss of consciousness. He was successfully managed with intravenous methylprednisolone, diphenhydramine, epinephrine, famotidine, and a fluid bolus. No further doses were administered due to disease progression. The patient underwent chimeric antigen receptor T-cell therapy, inducing a remission. It was then decided to proceed with allogeneic HSCT. Conditioning therapy consisted of total body irradiation and cyclophosphamide, both of which are associated with a high incidence of mucositis.^{10,11} In an effort to help prevent and mitigate this toxicity, the patient's parents inquired about the use of palifermin.

Despite the contraindication for use of palifermin in patients with known hypersensitivity to *E. coli*-derived proteins, it was decided to proceed with palifermin administration (1550 µg (60 µg/kg/dose) × 3 doses) by admitting the patient to the pediatric intensive care unit (PICU) to administer a 10% test dose (150 µg), followed by the remaining 90% (1350 µg), if no reaction occurred. We hypothesized that any HSR to palifermin would occur during this first fraction of the dose and that theoretically a less severe reaction would occur.

Palifermin (Kepivance; Biovitrum, Stockholm, Sweden) is supplied in 5 mg/mL vials. The 10% test dose was calculated as 0.03 mL, and the remaining 90% was 0.27 mL (total dose = 1550 µg). To ensure accuracy in drawing up such a small volume, our pharmacy department created a 1:10 dilution (500 µg/mL) with 0.9% normal saline (NS). The 10% test dose was then drawn up using 0.3 mL of the dilution and then further diluted with 0.9% NS for a final volume of 0.5 mL. The test dose was administered via intravenous push with emergency medications available at the bedside in case of HSR. Twenty minutes following the test dose, no reaction was observed; therefore, the remaining 90% of the dose was administered. Following 2 h of observation, he experienced neither an HSR nor anaphylaxis and he was discharged. He went on to successfully receive two more pre-conditioning doses and three post-conditioning doses without reaction. All subsequent injections were administered in full without the use of test doses. The patient did appear to receive benefit from palifermin administration as his mucositis

lasted only four days. He only received opioid pain medication for mucositis for five days. He was maintained on total parenteral nutrition for 21 days; however, this was largely due to nausea and emesis rather than mucositis.

Discussion

To our knowledge, this case report is the first describing the successful use of palifermin after an anaphylactic reaction to pegaspargase. This may suggest limited cross-reactivity between these two *E. coli*-derived products, despite the contraindication palifermin carries.^{2,5} Given that palifermin may improve mucositis during HSCT for pediatric patients, further investigation is warranted.²

The clinical quandary surrounding the use of palifermin in this patient was that we suspected that the Immunoglobulin E on his mast cells were already sensitized to *E. coli*-derived epitopes based on his prior reaction to pegaspargase. We acknowledge that patients can develop antibodies to both asparaginase and/or the polyethylene glycol (PEG) component of pegaspargase.^{3,12} We were, however, unable to test for PEG antibodies, as these assays are currently not available for commercial use. Due to this, it is indeterminate whether our patient developed hypersensitivity to the *E. coli*-derived epitopes or another component of the drug. If the patient developed antibodies to one of the other components, an allergic reaction to palifermin would not be expected. However, since *E. coli* epitopes are common to both pegaspargase and palifermin, a similar high fidelity hypersensitivity response should be elicited with palifermin administration. Additionally, pegaspargase is a native, purified *E. coli* enzyme that is covalently attached to a polymer with a very large molecular weight of 5000 kDa and is also given in large doses, thus making it a potential hapten.⁴ Anaphylaxis is a known adverse event, occurring more commonly with regular L-asparaginase than pegaspargase.³ Conversely, palifermin is a truncated 16 kDa, fully human recombinant protein that is produced in an *E. coli* vector-based system and then filtered, lyophilized, and sterilized.⁵ Immunogenicity and anaphylaxis have occurred with palifermin.^{3,6,8} Taking this into account, we theorized that the indirect evidence supported a conclusion that the antigens are mostly unrelated and no cross-reaction would occur. In this instance, the operative issue was whether palifermin, in its final reconstituted form, at a dose of 60 µg/kg/day, was substantial enough to cause a reaction.

One limitation to consider in this case report is the unknown stability of the diluted drug. Palifermin is a large protein molecule whose functional properties are dependent on its three-dimensional structure.¹⁻⁵

The drug comes with excipients such as histidine and polysorbate, whose function is to stabilize the protein. When making dilutions of the drug, these excipients are also diluted.⁵ Furthermore, albumin is occasionally recommended by drug manufacturers as the diluent of choice when making dilutions of proteins to aid in solution stabilization, to prevent adsorption to surfaces (i.e. plastic syringes), and to prevent precipitation.¹³ Therefore, NS may not have been the ideal vehicle for dilution of palifermin; however, in the absence of any specific guidance from the manufacturer on the creation or stability of a dilution, we assumed that NS was appropriate.⁵

This case report demonstrates a pediatric patient with history of a severe anaphylactic reaction to pegaspargase who was successfully treated with palifermin. We established that the drug could feasibly be diluted and administered as a 10% test dose, followed by observation for signs of HSR, prior to full dose administration. Palifermin and pegaspargase, despite both being derived from *E. coli* sources, are very different drugs in structure and composition with palifermin being a human growth factor and pegaspargase being an *E. coli* enzyme. Pairing this knowledge with what was observed in our patient, it can be concluded that palifermin can potentially be considered as supportive care therapy in patients with previous HSR/anaphylaxis to pegaspargase.

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Conflict of interest

None declared.

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