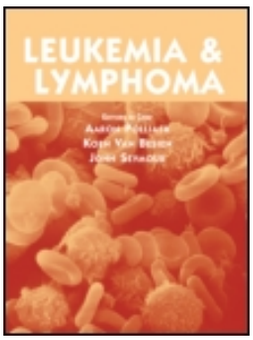

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Allergic reactions associated with pegaspargase in adults

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ABSTRACT

One of the severe toxicities of pegaspargase (PEG) is the development of allergic reactions. This study retrospectively assessed 311 PEG doses administered to 139 acute lymphoblastic leukemia patients from May 1, 2008 to July 30, 2014 for allergic reactions based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Fourteen reactions were recorded in 13 patients (9.4%). The rate of reaction did not differ between patients who received pre-medications and those who did not ($p = 0.939$). Patients who received only IV PEG doses had a higher rate of reaction compared to only IM PEG (14.0% vs 1.6%; $p = 0.010$). Six of the seven patients with CTCAE grade 4 reactions received a majority of IV doses, suggesting that severity of reactions may increase with IV administration. Capped doses at 3750 units only had a reaction rate of 2.3%, while uncapped doses over 3750 units were found to have a 6.0% reaction rate ($p = 0.194$).

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Introduction

E. coli L-asparaginase (ASP) is a crucial component of acute lymphoblastic leukemia (ALL) treatment regimens. ALL cells cannot synthesize the amino acid L-asparagine from L-glutamine due to low levels of asparagine synthase and the inability to up-regulate asparagine synthase. ASP hydrolyzes L-asparagine to L-aspartic acid and ammonia, depleting L-asparagine and resulting in cell death in the G1 phase. In the DFCI 77-01 trial, pediatric ALL patients were randomized to receive or not receive ASP as part of intensification. After a median of 9.4 years, event-free-survival was 71% with ASP and 31% without ASP.[1] There are no randomized studies in adults that directly compared outcomes with or without ASP. The GRAALL-2003 study treated adult ALL patients with an intensified regimen that included 16-fold more ASP, 3.7-fold more vincristine and 8.6-fold more prednisone compared to the previous LALA-94 regimen.[2] When retrospectively compared to the LALA-94 regimen, the 42-month event-free survival was improved from 33% to 57% and overall survival improved from 41% to 61%. However, one of the severe toxicities of ASP is the development of allergic reactions, which can limit future doses.

Pegaspargase (PEG), a polyethylene glycol conjugated asparaginase, has been used as an alternative to ASP and found to have equivalent response rates.[3,4] It was hypothesized that the conjugation to polyethylene glycol could decrease immunogenicity and increase the circulating half-life of the drug.[5] Patients with known allergic reactions to ASP could tolerate infusions of PEG without developing clinical reactions.[6,7] However, PEG still carries a rate of allergic reaction that ranges from 10–32%.[8]

ASP and derivatives have been incorporated into pediatric ALL regimens since the 1960s.[9] Initially, adult ALL trials minimized or avoided use of ASP due to toxicities. With the improvements in purity of the drug, introduction of PEG and increasing evidence that ASP is one of the best treatments for pediatric ALL, there has been renewed interest in exploring ASP and derivatives in adult patients.[10] In adults, PEG allergic reactions may be less frequent than in pediatrics, possibly due to the decreased number of doses per patient or possibly due to early reporting in adult protocols.[10,11]

In adults, it has also been reported that receiving $<80\%$ of the planned ASP doses significantly decreased 3-year overall survival and relapse-free survival.[12] The reasons reported for reduced ASP dosing included hypersensitivity reactions, pancreatitis and deterioration in performance status. Allergic reactions may also result in the production of neutralizing antibodies, which significantly diminishes the half-life of future PEG

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doses. The clinical significance of these neutralizing antibodies on efficacy of PEG is still unclear and debated.[13]

Due to the crucial role of PEG in ALL regimens, preventing allergic reactions could potentially improve survival. The goal of this study is to retrospectively assess the incidence of allergic reactions of PEG in adults at our institution, as well as compare the role of pre-medication, route of administration and dose-capping as factors that may affect the incidence of reactions.

Methods

In this retrospective, single-center study, adult ALL patients greater than 18 years of age who received at least one dose of PEG from May 1, 2008 to July 30, 2014 at Stanford Health Care were evaluated for allergic reactions. The start date of May 1, 2008 was chosen because it was when our institution first implemented our current electronic medical record (EMR) system. After Institutional Review Board approval, a list of all doses of PEG administered was obtained. Only patients that received PEG through intravenous (IV) or intramuscular (IM) route were included in the analysis.

Patient's demographics were collected from the EMR. Physician and nursing progress notes after each dose of PEG administered were reviewed for documentation of an allergic reaction to PEG. We also reviewed our institution's adverse event reporting system. The severity of each reaction was determined based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for allergic reactions (Supplemental Table I).[14] Data collected for each dose also included the route of administration (IV or IM), whether or not the dose was capped at 3750 units, and whether the dose was pre-medicated with acetaminophen, diphenhydramine and/or corticosteroid (dexamethasone, hydrocortisone, methylprednisolone or prednisone).

Comparisons of incidence of allergic reactions were analyzed using chi-square statistical tests with two-tailed *p*-values.

Results

A total of 311 PEG doses were administered to 139 patients during the study interval. The median age was 37 years old (range = 18–87 years). Fourteen reactions were recorded in 13 patients, resulting in a reaction in 9.4% of patients. A majority of patients were newly diagnosed ALL patients treated with CALGB 9511 protocol, followed by CALGB 10403 protocol.[15] Four patients relapsed on the first regimen and were subsequently treated with a second PEG-containing regimen. The median dose that patients experienced an allergic reaction was after receiving the third dose and the most common CTCAE grade was grade 4 reactions with seven (50%) of 14 reactions, followed by grade 2.

In the cohort, a total of 140 doses were found to be administered with all pre-medications (corticosteroid, acetaminophen, diphenhydramine), 63 doses were administered with no pre-medications and 94 doses were administered with any partial combination of pre-medications (e.g. acetaminophen, diphenhydramine, no corticosteroid). There were seven (4.8%), four (4.1%) and three (4.6%) reactions for doses that were administered with all pre-medications, partial pre-medications and no pre-medications, respectively. There was no significant difference in the rate of reaction ($p = 0.939$).

The route of administration was compared between individual doses and between patients. A total of 147 PEG doses were administered IV and 164 doses administered IM. Ten reactions (6.8%) were noted during an IV infusion, while four reactions (2.4%) were noted with IM injection. As individual doses, there was a non-significant trend toward higher incidence with IV administration ($p = 0.064$), but there was a statistically significant difference in incidence of grades 3–4 allergic reactions with IV administration ($p = 0.021$). Because patients received multiple doses of PEG, patients were divided into whether they received all IV, all IM or a combination of IV and IM doses. Patients who received all IV doses had a higher incidence of reactions ($n = 8$; 14.0%) compared to patients who received all IM doses ($n = 1$; 1.6%; $p = 0.010$).

Another factor examined was whether dose-capping at 3750 units affected incidence of allergic reactions. Patients who received doses above 3750 units were compared to patients who had a body surface-area that could warrant a dose greater than 3750 units, but were capped at 3750 units based on protocol. Reactions were noted in five patients (9.6%) of the 52 patients who were not dose-capped, while two reactions (4%) were noted in the 50 patients who were dose-capped. However, this was not statistically significant ($p = 0.285$). On a per dose basis, nine reactions (6.0%) were noted in the 149 doses greater than 3750 units, while only two reactions (2.3%) resulted in the 86 doses of 3750 units ($p = 0.194$).

Of the factors including pre-medication, route of administration and dose-capping, only the route of administration was found to be statistically significant. We examined the effect of the route of administration on the severity of the reaction. In the seven patients that had grade 4 reactions, five patients received exclusively IV doses, one patient received three IV and one IM dose and one patient received all IM doses.

Discussion

We examined whether pre-medication affected the incidence of allergic reactions. In the CALGB 10403 trial for newly-diagnosed adolescent and young adult ALL patients, the protocol was amended to recommend pre-medication with hydrocortisone, diphenhydramine and acetaminophen after 15% of the first 61 adult patients developed grade 3–4 allergic reactions.[10] However, case reports of anaphylactic reaction to PEG, even after pre-medication, have been reported in pediatric patients.[16] Interestingly, our study did not find a significant difference in allergic reactions for doses that were pre-medicated.

The route of administration may also affect PEG's rate of allergic reactions. PEG is FDA-approved for IM and IV infusion. IM administration of ASP has been shown to have decreased anaphylactic reactions compared to IV ASP.[17] However, data for PEG administration is conflicting. Two retrospective studies in pediatric patients have been published regarding IM vs IV administration of PEG. Pidaparti and Bostrom [18] found that allergic reactions developed in 17 of 186 (9%) patients receiving IM PEG and four of 11 (36%) patients receiving IV PEG ($p = 0.019$). The authors concluded that there was an increased incidence of allergic reactions in patients who receive IV PEG compared with IM, with similar severity. August et al. [19] evaluated 68 patients and found that the incidence of allergic reactions between IV PEG and IM PEG were not significantly different ($p = 0.25$). In our study, we found that adult patients who received all PEG doses as IV infusion reacted at a higher rate compared to patients who received all PEG doses as IM injection. The reactions of patients who received mostly IV doses of PEG also appeared to be more severe compared to patients who received mostly IM doses of PEG. This suggests that administering PEG through the IM route when possible may reduce the incidence of allergic reactions and reduce the severity of reactions in patients. One patient experienced a grade 3 reaction with his first dose of PEG, which was administered IV. After careful consideration, it was decided to re-challenge PEG by IM route. The patient received four IM doses without any incident.

We also evaluated the effect dose-capping has on allergic reactions. In ASP, the incidence of allergic reactions have been found to increase with doses greater than 6000 units/m^2.[20] However, there is no published data on whether larger doses of the PEG formulation increase the incidence of allergic reactions. Protocols differ in the dose of PEG, with some protocols dose-capping at 3750 units. By comparing doses greater than 3750 units to doses capped at 3750 units, we found a non-significant trend toward a higher incidence of reactions with the larger doses. This may be confounded by differences in population. Pediatric-inspired protocols for adolescents and young adults (e.g. CALGB 10403) often do not dose-cap PEG, while the protocols for older adults (e.g. CALGB 9511) often dose-cap.

There are many limitations to our study. Because our study was not prospective, we relied on self-reporting to detect allergic reactions. This may bias towards more severe reactions or reactions that required interventions. Also, because many doses of PEG were administered in the outpatient infusion center, delayed allergic reactions may have been under-reported. At our institution, patients are routinely monitored for ~1 h after administration of chemotherapy, so any reactions happening after the patient leaves the infusion center may not be documented, especially if they do not require any intervention. Another limitation of this study is that we were unable to examine patients' prior exposure to ASP. Some of the patients who relapsed may have received ASP previously from another hospital. However, because many patients are referred to our hospital after relapse, their complete records are not in our EMR. Additionally, the majority of ASP doses were ordered before the implementation of our current EMR.

Conclusion

To our knowledge, this is the first study to retrospectively evaluate factors that affect PEG allergic reactions in adults. We found that 9.4% of patients receiving PEG experienced allergic reactions, most commonly after the third dose, which is also consistent with previously published studies. We found IV administration of PEG has a higher rate of allergic reactions in adult patients compared to IM administration. Additionally, allergic reactions appear to be more severe with IV administration. Because of the importance of PEG in ALL treatment regimens, further study evaluating the different routes of administration's impact on survival is warranted.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.3109/10428194.2015.1105369.

References

[1] Sallan SE, Gelber RD, Kimball V, et al. More is better! Update of Dana-Farber Cancer Institute/Children's Hospital childhood acute lymphoblastic leukemia trials. Haematol Blood Transfus 1990; 33: 459–466.

[2] Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol 2009; 27: 911–918.

[3] Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001; 97: 1211–1218.
[4] Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. Blood 2002; 99: 1986–1994.
[5] Park YK, Abuchowski A, Davis S, et al. Pharmacology of Escherichia coli-L-asparaginase polyethylene glycol adduct. Anticancer Res 1981; 1: 373–376.
[6] Ettinger LJ, Kurtzberg J, Voute PA, et al. An open-label, multicenter study of polyethylene glycol-L-asparaginase for the treatment of acute lymphoblastic leukemia. Cancer 1995; 75: 1176–1181.
[7] Kurtzberg J, Asselin B, Bernstein M, et al. Polyethylene Glycol-conjugated L-asparaginase versus native L-asparaginase in combination with standard agents for children with acute lymphoblastic leukemia in second bone marrow relapse: a Children's Oncology Group Study (POG 8866). J Pediatr Hematol Oncol 2011; 33: 610–616.
[8] Graham ML. Pegaspargase: a review of clinical studies. Adv Drug Deliv Rev 2003; 55: 1293–1302.
[9] Dolowy WC, Henson D, Cornet J, et al. Toxic and antineoplastic effects of L-asparaginase. Study of mice with lymphoma and normal monkeys and report on a child with leukemia. Cancer 1966; 19: 1813–1819.
[10] Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011; 52: 2237–2253.
[11] Rytting M. Peg-asparaginase for acute lymphoblastic leukemia. Expert Opin Biol Ther 2010; 10: 833–839.
[12] Storring JM, Minden MD, Kao S, et al. Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. Br J Haematol 2009; 146: 76–85.
[13] Zeidan A, Wang ES, Wetzler M. Pegasparaginase: where do we stand? Expert Opin Biol Ther 2009; 9: 111–119.
[14] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services; June 14, 2010.
[15] Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. Blood 2007; 109: 4164–4167.
[16] Sahiner UM, Yavuz ST, Gokce M, et al. Anaphylactic reaction to polyethylene-glycol conjugated-asparaginase: premedication and desensitization may not be sufficient. Pediatr Int 2013; 55: 531–533.
[17] Nesbit M, Chard R, Evans A, et al Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. Am J Pediatr Hematol Oncol 1979; 1: 9–13.
[18] Pidaparti M, Bostrom B. Comparison of allergic reactions to pegasparaginase given intravenously versus intramuscularly. Pediatr Blood Cancer 2012; 59: 436–439.
[19] August KJ, Miller WP, Dalton A, et al. Comparison of hypersensitivity reactions to PEG-asparaginase in children after intravenous and intramuscular administration. J Pediatr Hematol Oncol 2013; 35: e283–286.
[20] Narta UK, Kanwar SS, Azmi W. Pharmacological and clinical evaluation of L-asparaginase in the treatment of leukemia. Crit Rev Oncol Hematol 2007; 61: 208–221.