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Case Report

Successful rechallenge with Erwinia chrysanthemi asparaginase after pegaspargase-induced hypertriglyceridemia: a case report

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***Abstract*:** Polyethylene-glycolated *Escherichia coli*-derived L-asparaginase (pegaspargase, pASP) is an essential component of paediatric-inspired regimens for the treatment of acute lymphoblastic leukaemia/lymphoma; nonetheless, is characterised by severe and potentially life-threatening toxicities, such as hypertriglyceridemia. Grades 3–4 events have been reported in ~1%–18% of paediatric patients and in sparse reports in adults. There is limited evidence on the safety of asparaginase rechallenge in patients experiencing severe pASP-related hypertriglyceridemia. Herein we present the case of a young adult patient diagnosed with T-LBL who experienced an asymptomatic severe pASP-related hypertriglyceridemia and was safely re-exposed to ASP using Erwinia chrysanthemi asparaginase (crisantapase), with only mild transient hypertriglyceridemia recurrence.

Keywords: ALL, hypertriglyceridemia, LBL, pASP, rechallenge

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Introduction

L-Asparaginase (ASP) plays a pivotal role in the context of paediatric-inspired regimens for the treatment of acute lymphoblastic leukaemia/lymphoblastic lymphoma (ALL/LBL) in adolescents and young adults (AYAs), as extensively shown.[1–8] Polyethylene-glycolated *Escherichia coli*-derived L-asparaginase (pegaspargase, pASP) has become the preferred asparaginase formulation due to its favourable pharmacokinetic profile compared to native formulations.[9] On the other hand, the use of pASP has been associated with severe and – although rarely – potentially life-threatening toxicities (e.g. hypersensitivity reactions, hepatotoxicity, hyperglycaemia, thromboembolism, pancreatitis, osteonecrosis and neurotoxicity).[10–12] Hypertriglyceridemia is a well-known adverse event, potentially leading to life-threatening end-organ damage. Severe hypertriglyceridemia (triglycerides >1000 mg/dL) has been reported in adult patients treated with pASP,[13–23] but several prospective studies reported ~1%–18% incidence of grades 3–4 events in paediatric patients and young adults.[24–27] Its pathophysiology and risk factors are not completely understood, although genetic predisposition appears to play a role[28] as well as a personal history of metabolic syndrome or hypothyroidism. Furthermore, older age and higher cumulative doses of steroid and pASP have been reported as significant risk factors.[29] Clinical management usually includes dietary modifications and administration of lipid-lowering agents such as fenofibrate and omega-3 fatty acids. There is no general consensus on the safety of asparaginase rechallenge in patients experiencing severe hypertriglyceridemia following pASP exposure. Even though sparse clinical reports have reported the outcome of patients undergoing pASP re-exposure,[30] there is no clear indication on how (i.e. full dose vs

reduced dose) and when it should be done. Limited evidence suggests a lower likelihood of hypertriglyceridemia when native, non-pegylated ASP formulations are used.[31]

Clinical case

Here, we present the case of an young adult patient diagnosed with T-cell LBL (T-LBL) treated with paediatric-inspired intensive chemotherapy according to the GIMEMA ALL1913 protocol who developed severe pASP-related hypertriglyceridemia and was safely re-exposed to ASP using Erwinia chrysanthemi asparaginase (crisantapase), with only mild hypertriglyceridemia recurrence.

In January 2023, a 25-year-old male patient, with no past medical history except for asymptomatic cholelithiasis and a personal and family history of hypothyroidism, was referred to our institution following the detection of a bulky mediastinal mass causing mediastinal syndrome and right vocal cord palsy. Histopathological examination of an excisional biopsy was consistent with T-LBL with a cortical, double-positive immunophenotype (TdT^+, $CD1a^+$, $CD4^+$, $CD8^+$). Cytogenetic analysis by fluorescent in situ hybridisation and copy number analysis on tissue samples from the mediastinal biopsy led to the identification of a t(7;9)(q34;q34) indicative of TRB@::NOTCH1 fusion, deletion of CDKN2AB/9p21, and CASP8AP2-GRIK2/6q14-15. Bone marrow evaluation was negative for leukemic cell infiltration. Baseline CNS status was negative. The patient underwent paediatric-inspired intensive chemotherapy according to the GIMEMA ALL1913 protocol for a total of four cycles, with concomitant triple intrathecal prophylaxis and achieved an early metabolic complete response by 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) scan. Treatment was overall well tolerated. Two pASP doses were administered in cycles 1 and 2 according to the protocol (1500 and 2000 UI/mq, respectively), without significant dose reduction in the absence of liver steatosis, obesity or other risk factors and with the occurrence of only slight G2 hyperbilirubinemia and transaminitis after the first dose. pASP-related hypofibrinogenemia and decrease in antithrombin activity were managed according to the recommendations.[2–4]

In June 2023, cycle 5 according to the GIMEMA ALL1913 protocol was initiated. Together with high-dose methotrexate and 6-mercaptopurine, pASP was administered at the dose of 2000 UI/m^2 (3700 UI) on day 3 of the cycle, without the occurrence of immediate adverse events. Three weeks after pASP administration, during a scheduled blood test, the laboratory reported the serum to be lipemic, causing interference with the measurement of routine blood biochemical tests. Further examinations showed severe hypertriglyceridemia [maximum value: 3575 mg/dL, upper limit of normal (ULN): 150 mg/dL] and hypercholesterolemia (maximum value: 395 mg/dL, ULN: 200 mg/dL). The patient did not report any food intake modification in the last few weeks and was totally asymptomatic. No signs of organ damage were detected. Lipase value was within normality range (lipase maximum value: 91 mg/dL, ULN: 200 U/L). L-carnitine 2 g BID intramuscularly for 5 days, fenofibrate 145 mg/day orally and omega-3 1000 mg TID orally were started, leading, together with the adoption of a low-fat diet, to a quick normalisation of the lipid profile. Four weeks after pASP administration, triglycerides and cholesterol were back to normal levels (triglycerides 146 mg/dL; total cholesterol 189 mg/dL); thus, L-carnitine and fenofibrate were stopped.

As soon as haematopoietic recovery was achieved, the patient transitioned to cycle 6 according to GIMEMA ALL1913 protocol, which would involve further pASP (2000 UI/m^2) administration along with multiagent intensive chemotherapy. In order to avoid potentially detrimental dose reductions and maintain appropriate ASP exposure, we opted for a switch to crisantapase, in consideration of its shorter half-life – which would have allowed us monitoring of the triglyceride level more closely – and the evidence of lower incidence of metabolic adverse compared to non-pegylated ASP formulations.[31] Omega-3 fatty acids prophylaxis was prosecuted until the end of the cycle. Treatment with crisantapase (25,000 UI/m^2 intravenously for six doses on days 8, 10, 12, 15, 17 and 19) was complicated by G3 nausea and vomiting requiring rescue with olanzapine 5 mg/day orally, significant diet modification. The patient experienced only a transient and moderate elevation of triglycerides (one abnormal value of 507 mg/dL was reported 3 days

after the last dose, soon returned to normal within 4 days) and no significant elevation in total cholesterol values (maximum value: 187 mg/dL). Grade 1 hyperbilirubinemia was observed. The patient was able to proceed and complete his treatment plan and is currently in ongoing complete remission. Eventually, his cholelithiasis became symptomatic and required elective cholecystectomy. It is unclear whether underlying abnormalities in lipids and/or biliary acids metabolism could have contributed to the occurrence of severe hypertriglyceridemia in our patient.

Conclusion

As pASP-containing regimens have definitely taken the lead in the treatment of AYA and adult patients with ALL/LBL, the problem of drug-induced toxicities – even more important in the adult population compared to the paediatric scenario – has become a concern. Severe hypertriglyceridemia is an underestimated pASP-induced adverse event, sometimes contributing to the occurrence of life-threatening end-organ damage – primarily osteonecrosis and thrombosis, and less commonly pancreatitis, as previously reported.[12,31] The mechanism through which pASP leads to hypertriglyceridemia is not completely understood; however, some authors reported an asparaginase-induced decrease in lipoprotein lipase activity.[31] On the other hand, corticosteroids are known to induce triglyceride synthesis, thus contributing to the occurrence of this adverse event when administered together. The incidence of grade 4 hypertriglyceridemia (>1000 mg/dL) have been reported to be less evident with pegylated versus native formulations, although the reasons for a more pronounced triglyceride elevation induced by pASP has not been clarified yet. The experience in this single case supports the feasibility of rechallenge with crisantapase after pASP-induced hypertriglyceridemia. Notably, in our patient, the first crisantapase dose was given only 6 weeks apart from the previous pASP dose, without dose reductions. Ultimately, switching to crisantapase allowed us to preserve appropriate ASP dose intensity without the reappearance of severe metabolic toxicity. Such a strategy could be worth considering in the relatively infrequent clinical scenario of pASP-induced severe hypertriglyceridemia.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication has been acquired from the patients whose clinical picture is described in this report.

Author contributions

Gaia Ciolli: Conceptualization; Data curation; Investigation; Methodology; Resources; Validation; Writing – original draft.

Andrea Pasquini: Conceptualization; Data curation.

Francesco Mannelli: Conceptualization; Data curation; Investigation; Methodology; Resources; Supervision; Validation; Writing – review & editing.

Barbara Scappini: Data curation; Investigation; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials
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