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Treatment of AYA/adult patients with ALL – The central role of asparaginase

Webinar Highlights

Speaker: Dr Nicola Gökbuget

Dr Nicola Gökbuget is the head of the study center at the department of hematology/oncology and the University Cancer Center (UCT) in Frankfurt, Germany, and one of the UCT Scientific Task Force directors.

She is also a principal investigator of the German Consortium for Translational Cancer Research and the Frankfurt Cancer Institute, a board member of the German and European LeukemiaNet as well as a founding member of the European Working Group for Adult ALL.

Dr Gökbuget has been a coordinator of the German Multicenter Study Group for Adult ALL (GMALL) for over 25 years, acting as principal investigator of several clinical trials in adult ALL and related hematological diseases. She has also established a national ALL registry in Germany.

In her research, Dr Gökbuget focuses on several clinical aspects of adult ALL. These include diagnosis, (MRD-based) treatment, quality-of-life outcomes, late effects, and the evaluation of potential new therapies and drugs, in both newly diagnosed as well as R/R settings.

The content of the webinar reflects the personal experiences and opinion of the presenter. All treatment-related statements are not necessarily in line with the approved product labels in all countries. Please consult your local Product Information for full details.

ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; MRD, minimal residual disease; R/R relapsed/refractory.

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Efficacy and tolerability of asparaginase in AYA/adult patients with ALL: The GMALL experience

More than 5000 patients across >150 hospitals have been treated with PEG-asparaginase as part of the GMALL protocols[1]

- In the GMALL 08/2013 trial, 3-year OS was 76% in patients aged 18-55 years[2]
- Intensification of PEG-ASP in consolidation and MRD-based blinatumomab were linked with a significantly improved OS in patients aged ≥55 years treated on pediatric-inspired, age-adapted GMALL protocols (P<0.0001)[3]

- Liver toxicity was the most common asparaginase-associated grade 3/4 toxicity in patients aged 18-55 years treated with either 500 or 2000 IU/m2* PEG-ASP during induction on GMALL 08/2013[4]
- Based on unpublished GMALL data and data from other groups, patients with BMI >30 and/or liver steatosis have an increased risk of liver toxicity

In the earlier GMALL 07/2003 protocol, a particularly pronounced improvement in OS was observed in patients aged 15-55 years with SR ALL receiving intensified PEG-ASP vs standard dosing (3-year OS 80% vs 68%, P<0.02)[5]

Asparaginase-associated toxicities in adult patients with ALL

The risk of developing certain asparaginase-associated toxicities increases with age (adults vs children)[6]

Hepatic toxicity is the most common AE observed in adult patients treated with ASP, but may also be enhanced by other complications such as infections and multiple comedications[1]

The incidence of hypertriglyceridemia may be underestimated in adults as triglycerides are often not measured[1]

A correlation between osteonecrosis and hyperlipidemia has been reported; microthromboses in the bone are one potential pathogenetic mechanism[1,8]

- Pancreatitis may manifest as a broad spectrum of symptoms, ranging from mild to severe, and a complete diagnostic confirmation and classification is important[1,9]
- Re-exposure to asparaginase after asparaginase-associated pancreatitis (AAP) has been associated with severe second AAP in almost half of patients and is therefore controversial, particularly in cases of severe pancreatitis[10,11]

Prophylaxis for venous thromboembolism includes LMWH and ATIII substitution[12]

Key messages

- Treatment of adult patients with PEG-ASP can be associated with improved survival outcomes
- A rational management of ASP-associated toxicities should be established and subject to continuous improvement and education in order to deliver optimal individualised doses for patients

***Please note that the approved dose of pegaspargase is 2500 IU/m² every 14 days in patients with a BSA ≥0.6 m² and who are ≤21 years of age, and 2000 IU/m² every 14 days in patients who are >21 years of age.**

AE, adverse event; AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; (PEG)ASP, (pegylated) asparaginase; ATIII, antithrombin III; AYA, adolescent/young adult; BMI, body mass index; BSA, body surface area; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; LMWH, low-molecular-weight heparin; MRD, minimal residual disease; OS, overall survival; SR, standard risk.

1. Dr Gökbuget, personal experience; 2. Gökbuget N et al. *Blood*. 2021;138(suppl 1):362; 3. Gökbuget N et al. *Blood*. 2022;140(suppl 1):121-123; 4. GMALL, unpublished data; 5. Gökbuget N et al. *Blood*. 2010;116 (21):494; 6. Toft N et al. *Leukemia*. 2018;32(3):606-615; 7. Mogensen SS et al. *Pediatr Blood Cancer*. 2018;65:e27300; 8. Schmiegelow K, et al. *F1000Res*. 2017;6:444; 9. Wolthers BO et al. Lancet Oncol. 2017;18(9):1238-1248; 10. Rank CU et al. J Clin Oncol. 2020;38:145-154; 11. Zwicker JI et al. *J Thromb Haemost*. 2020;18:278-284.

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Insights from the expert's clinical practice[1]

In the GMALL 08/2013 protocol, has the use of PEG-asparaginase during maintenance been associated with added benefits and/or toxicity?

"In the GMALL 08/2013 trial, 9 doses of PEG-asparaginase were scheduled for first-line treatment and we tried to add another 6 doses during maintenance. This part was stopped early, because less than 50% of the patients were able to achieve the fully scheduled doses of asparaginase in maintenance. This was a stop criterion for this approach as per protocol. I think in a protocol like ours, which already comprises high and frequent dosing of PEG-asparaginase, additional use of asparaginase in maintenance is not necessary."

Is there any difference in the rate of thrombosis between different types of asparaginase?

"If asparaginase is adequately dosed*, the same incidence of toxicities can be expected with different asparaginase formulations (native E. coli asparaginase, Erwinase and PEG-asparaginase). I am not aware of any specific data on thrombosis. Any comparisons would be difficult because native preparations are often stopped in case of toxicities. Furthermore, measures for thrombosis prophylaxis may vary."

You mentioned that hypertriglyceridemia may be underdiagnosed. Would you recommend regular hypertriglyceridemia measurements?

"I would recommend measuring triglycerides during asparaginase treatment and expected duration of activity. Hypertriglyceridemia may contribute to the development of osteonecrosis. The mechanism of action is not entirely clear; osteonecrosis is linked to the use of steroids, but there may be an increased risk with a simultaneous use of asparaginase and while asparaginase activity persists. The GMALL group generally questions every use of steroids in ALL and recommend discontinuing steroids whenever possible and not part of the primary treatment."

In your clinical practice, do you routinely prescribe anti-allergic pre-medication prior to asparaginase treatment?

"It is not always easy to differentiate between real allergic reactions and infusion reactions. If it is a very severe reaction with systemic symptoms, we usually stop the use of PEG-asparaginase and shift to a second-line preparation such as Erwinase. In less severe reactions, such as an infusion reaction, it may be an option to expand the infusion time or try anti-allergic premedication. The problem with premedication is that it can mask an allergic reaction, which leads to an inactivation of asparaginase. Therefore, it is very important if we use premedication that an activity measurement takes place."

***Please note that the approved dose of pegaspargase is 2500 IU/m² every 14 days in patients with a BSA ≥0.6 m² and who are ≤21 years of age, and 2000 IU/m² every 14 days in patients who are >21 years of age.**

ALL, acute lymphoblastic leukemia; BSA, body surface area; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; LMWH, low-molecular-weight heparin; PEG, pegylated.

1. Gökbuget N. *Treatment of AYA/adult patients with ALL – The central role of asparaginase.* Webinar and Q&A sessions, April 25 and 27, 2023.

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ONCASPAR®

COMPOSITION* Solution for injection/infusion: One ml of solution contains 750 Units (U) of pegaspargase. One vial of 5 ml solution contains 3,750 Units.** Powder for solution for injection/infusion: Each vial contains 3,750 Units (U) of pegaspargase. After reconstitution, 1 ml of solution contains 750 U pegaspargase (750 U/ml).*** INDICATIONS* Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients. DOSAGE AND ADMINISTRATION* Oncaspar should be prescribed and administered by physicians and/or health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available. Oncaspar is usually administered as part of combination chemotherapy protocols with other antineoplastic agents. Recommended premedication: Premedicate patients with paracetamol, an H-1 receptor blocker (e.g. diphenhydramine), and an H-2 receptor blocker (e.g. famotidine) 30-60 minutes prior to administration of Oncaspar to decrease the risk and severity of both infusion and hypersensitivity reactions. Paediatric patients and adults ≤ 21 years of age: The recommended dose in patients with a body surface area (BSA) ≥ 0.6 m2 and who are ≤ 21 years of age is 2,500 U of pegaspargase (equivalent to 3.3 ml Oncaspar)/ m2 body surface area every 14 days. Children with a body surface area <0.6 m2 should receive 82.5 U of pegaspargase (equivalent to 0.1 ml Oncaspar)/kg body weight every 14 days. Adults > 21 years of age: Unless otherwise prescribed, the recommended posology in adults aged > 21 years is 2,000 U of pegaspargase (equivalent to 2.67 ml Oncaspar)/ m2 body surface area every 14 days. Oncaspar can be given by intramuscular (IM) injection or intravenous (IV) infusion. For smaller volumes, the preferred route of administration is intramuscular. When Oncaspar is given by intramuscular injection, the volume injected at one site should not exceed 2 ml in children and adolescents, and 3 ml in adults. If a higher volume is given, the dose should be divided and given at several injection sites. Intravenous infusion of Oncaspar is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution. Do not infuse other medicinal products through the same intravenous line during administration of Oncaspar. CONTRAINDICATIONS* Hypersensitivity to the active substance or to any of the excipients. Severe hepatic impairment (bilirubin >3 times upper limit of normal [ULN]; transaminases >10 times ULN). History of serious thrombosis with prior L-asparaginase therapy. History of pancreatitis, including pancreatitis related to previous L-asparaginase therapy. History of serious haemorrhagic events with prior L-asparaginase therapy. WARNINGS* *Asparaginase antibodies*: The presence of anti-asparaginase antibodies may be associated with low asparaginase activity levels due to potential neutralising activity of these antibodies. *Hypersensitivity*: Hypersensitivity reactions, including life-threatening anaphylaxis, can occur during therapy, including in patients with known hypersensitivity to *E. coli* derived asparaginase formulations. Premedicate patients 30-60 minutes prior to administration of Oncaspar. Other hypersensitivity reactions can include angioedema, lip swelling, eye swelling, erythema, decreased blood pressure, bronchospasm, dyspnoea, pruritus and rash. Oncaspar should be discontinued in patients with serious hypersensitivity reactions. *Pancreatic effects*: Pancreatitis, including haemorrhagic or necrotising pancreatitis with fatal outcomes, has been reported. Patients should be informed of the signs and symptoms of pancreatitis which, if left untreated, could become fatal. If pancreatitis is suspected, Oncaspar should be discontinued; if pancreatitis is confirmed, Oncaspar should not be restarted. *Coagulopathy*: Serious thrombotic events, including sagittal sinus thrombosis can occur. Oncaspar should be discontinued in patients with serious thrombotic events. Coagulation parameters should be monitored at baseline and periodically during and after treatment. *Osteonecrosis*: In the presence of glucocorticoids, osteonecrosis (avascular necrosis) is a possible complication of hypercoagulability observed in children and adolescents with a higher incidence seen in girls. A close monitoring in children and adolescents' patients is recommended. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. *Hepatic effects*: Combination therapy with Oncaspar and hepatotoxic products can result in severe hepatic toxicity. Caution is required when Oncaspar is given in combination with hepatotoxic products, especially if there is pre-existing hepatic impairment. Patients should be monitored for changes in liver function parameters. *Central nervous system effects*: Combination therapy with Oncaspar can result in central nervous system toxicity. Cases of encephalopathy (including reversible posterior leukoencephalopathy syndrome) have been reported. Oncaspar may cause central nervous system signs and symptoms manifesting as somnolence, confusion, convulsions. Patients should be closely monitored for such symptoms, especially if Oncaspar is used in association with neurotoxic products (such as vincristine and methotrexate). *Myelosuppression*: Pegaspargase may cause myelosuppression, either directly or indirectly. Use of Oncaspar could increase the risk of infections. *Hyperammonaemia*: Intravenous administration of asparaginase may cause serum levels of ammonia to rise sharply following administration. The symptoms of hyperammonaemia are often transient and can include: nausea, vomiting, headache, dizziness and rash. In severe cases, encephalopathy can develop with or without hepatic impairment, especially in older adults, which can be life-threatening or fatal. If symptoms of hyperammonaemia exist, ammonia levels should be monitored closely. *Contraception*: An effective non-oral method of contraception must be used during Oncaspar treatment and for at least 6 months after discontinuation. *Excipients*: contain sodium (less than 1 mmol sodium (23 mg) per dose, that is to say, essentially 'sodium-free'). INTERACTION(S)* *Caution*: The decrease in serum proteins caused by pegaspargase can increase the toxicity of other medicinal products that are protein bound. Methotrexate and cytarabine can interact differently with Oncaspar: their prior administration can increase the action of pegaspargase synergistically. Pegaspargase can interfere with metabolism and clearance of other medicinal products, based on its effects on protein synthesis and hepatic function, as well as from its combined use with other chemotherapy products known to interact with CYP enzymes. The use of Oncaspar can lead to fluctuation in coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Caution is therefore needed when anticoagulants such as coumarin, heparin, dipyridamole, acetylsalicylic acid or non-steroidal anti-inflammatory medicinal products are given concomitantly, or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered. When glucocorticoids (e.g., prednisone) and pegaspargase are given at the same time, alterations in coagulation parameters (e.g., fall in fibrinogen and antithrombin III deficiency, ATIII) can be more pronounced. Pegaspargase may increase the risk of glucocorticoid- induced osteonecrosis in children and adolescents when both treatments are given simultaneously, with a higher incidence seen in girls, through a potential increase in exposure of dexamethasone. Immediately preceding or simultaneous treatment with vincristine can increase the toxicity of pegaspargase. Administration of Oncaspar before vincristine may increase the neurotoxicity of vincristine. Vincristine should be given at least 12 hours prior to administration of Oncaspar. Simultaneous vaccination with live vaccines may increase the risk of severe infections attributable to the immunosuppressive activity of pegaspargase, the presence of the underlying disease and combination chemotherapy. Vaccination with live vaccines should therefore be given no earlier than 3 months after termination of the entire antileukaemic treatment. *Not recommended*: An indirect interaction cannot be ruled out between pegaspargase and oral contraceptives due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the concomitant use of Oncaspar with oral contraceptives is not recommended. Another method than oral contraception should be used in women of childbearing potential. FERTILITY* PREGNANCY* Not recommended. BREASTFEEDING* Breast-feeding should be discontinued during treatment with Oncaspar and should not be restarted until after discontinuation of Oncaspar. CONTRACEPTION* Men and women should use effective contraception during treatment and for at least 6 months after Oncaspar discontinuation. A method other than oral contraception should be used in women of childbearing potential. DRIVE & USE MACHINES* Somnolence, confusion, dizziness, syncope, seizure have been reported. UNDESIRABLE EFFECTS* *Very common*: Febrile neutropenia, pancreatitis, diarrhoea, abdominal pain, nausea, hypersensitivity, urticaria, anaphylactic reaction, weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, lipase increased, amylase increased, activated partial thromboplastin time prolonged, blood bilirubin increased, decreased appetite, hyperglycaemia, rash, embolism. *Common*: Anaemia, coagulopathy, vomiting, stomatitis, ascites, hepatotoxicity, fatty liver, infections, sepsis, prothrombin time prolonged. International normalised ratio increased, hypokalaemia, blood cholesterol increased, hypofibrinogenaemia, gammaglutamyl transferase increased, hyperlipidaemia, hypercholesterolaemia, pain in extremities, seizure, peripheral motor neuropathy, syncope, hypoxia, thrombosis. Rare: Pancreatitis necrotising, pancreatitis haemorrhagic, hepatic necrosis, jaundice, cholestasis, hepatic failure, posterior reversible leukoencephalopathy syndrome. *Not known*: Bone marrow failure, pancreatic pseudocyst, parotitis, pyrexia, anaphylactic shock, blood urea increased, anti-pegaspargase antibodies, neutrophil count decreased, platelet count decreased, hyperammonaemia, diabetic ketoacidosis, hypoglycaemia, osteonecrosis, somnolence, tremor, confusional state, renal failure acute, toxic epidermal necrolysis, cerebrovascular accident, haemorrhage, superior sagittal sinus thrombosis. OVERDOSE* PROPERTIES* L-asparaginase is the enzymatic cleavage of the amino acid L-asparagine into aspartic acid and ammonia. Depletion of L-asparagine in blood results in inhibition of protein-synthesis, DNA-synthesis and RNA-synthesis, especially in leukaemic blasts which are not able to synthesise L-asparagine, thus undergoing apoptosis. PRESENTATION* Pack size of 1 vial with 5 ml solution** Pack size of 1 vial.*** MARKETING AUTHORISATION HOLDER LES LABORATOIRES SERVIER, 50 rue Carnot, 92284 Suresnes cedex France. www.servier.com.

*For complete information, please refer to the Summary of Product Characteristics for your country.

** *Applicable only to Oncaspar, solution for injection.*

*** *Applicable only to Oncaspar, powder for injection/infusion.*

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