GUIDELINE ARTICLE

Recognition, prevention, and management of adverse events associated with asparaginase/pegaspargase treatment of acute lymphoblastic leukemia in adults: consensus of an expert panel

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Recognition, prevention, and management of adverse events associated with asparaginase/pegaspargase treatment of acute lymphoblastic leukemia in adults: consensus of an expert panel: Supplement 1

Methods

Determination of ASNase-associated toxicities and AEs as the topic of consensus statement; panel recruitment; and vetting

A group of medical experts who manage adult ALL patients and incorporate ASNase into their treatment regimens suggested reviewing the AEs associated with ASNase therapy in adult ALL patients as a basis for a consensus statement that aims to improve the safety and tolerance of and compliance with the use of this therapy in this population. The consensus panel leaders (chair and co-chairs) were selected, and panel membership was strategically selected to ensure global representation. The potential panelists were invited by the chair and informed of the requirements and desired qualifications for panel membership. Once the panel was assembled, members disclosed potential conflicts of interest, which were vetted by the chair and co-chairs. The panel chair and two co-chairs led the development of the clinical statements using a modified Delphi methodology with input from a methodologist.

Literature review and determination of the consensus statement scope

Two systematic biomedical literature searches produced relevant publications published between April 2009 and April 2024. Search criteria (Supplement Table 1) were established using the patient, intervention, comparison, outcome, timeframe, and setting [PICO(TS)] format (Supplement Table 2). The literature searches guided the panel in drafting clinical consensus statements that could help fill evidence gaps for evaluation and included systematic reviews (including meta-analyses), clinical practice guidelines, randomized controlled trials (RCTs), observational studies, and other relevant studies or publications in English. The gaps identified from the literature search results formed the framework for the Delphi surveys.

The panel made several decisions about the scope of the clinical consensus statements before formally implementing the Delphi method. First, the panel identified hepatotoxicity, hypersensitivity

reactions/infusion-related reactions (HSRs/IRRs), thromboembolic/coagulation complications, pancreatitis/metabolic complications, and dosing as topics of interest. Second, the panel used the literature search results to prioritize the topics that could benefit from potential consensus from an expert panel. Finally, these topics were used to formulate the initial statements evaluated using the Delphi method.

Delphi method and administration

The panel used a modified Delphi method to distill expert opinion into concise clinical consensus statements. This rigorous and standardized method uses multiple anonymous surveys to minimize bias and facilitate expert consensus. The panel members used a web-based software program (www.surveymonkey.com) to execute the confidential surveys. All answers were presented anonymously and remained confidential; however, names were collected to ensure proper follow-up if needed.

The panel chair and co-chairs developed both Delphi surveys. Before dissemination to the panel, the surveys were reviewed by a methodologist for content and clarity. Questions in the survey were answered using a 9-point Likert scale with the following anchors (1=strongly disagree, 3=disagree, 5=neutral, 7=agree, 9=strongly agree). The surveys were completed by the panelists, and responses were aggregated, distributed, discussed by teleconference, and revised by the panelists as warranted. The purpose of the teleconference(s) was to clarify any ambiguity, discuss proposed revisions, and, if needed, discard statements. The criteria for consensus were established *a priori* with reference to previous consensus statements (outliers were defined as any rating at least 2 Likert points away from the mean) (Supplement Table 3).[1,2]

Two iterations of the Delphi method survey were performed. The panel extensively discussed (by virtual meetings) the results of each item after the first survey. Items that reached consensus were accepted, and items that did not meet consensus were discussed further to determine if wording or specific

language contributed to the lack of consensus. The second iteration of the survey was used to reassess items that reached near-consensus or wording that had been significantly altered. The expert panel then discussed (by teleconference) the results of the second survey. All items reaching consensus were accepted; the items not reaching consensus were not attributed to wording and other modifiable factors but rather to a true lack of consensus.

The expert panel grouped the final versions of the clinical consensus statements into 5 specific categories: 1) hepatotoxicity; 2) HSRs/IRRs; 3) thromboembolic/coagulation complications; 4) pancreatitis/metabolic complications; and 5) dosing. The final manuscript was drafted with participation of and final review from each panel member.

Supplemental References

1. Mitchell RB, Hussey HM, Setzen G, et al. Clinical consensus statement: tracheostomy care. *Otolaryngol Head Neck Surg*. 2013;148(1):6-20. doi:10.1177/0194599812460376

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Supplement Table 1. Key Search Terms	
Anaphylaxis	Hyperbilirubinemia
Asparaginase	Hyperlipidemia
Asparagine amidohydrolase	Hypersensitivity
Asparagine depletion	Hypertriglyceridemia
Bleed	Infusion reaction
Calaspargase	Levocarnitine
Coagulopathy	Metabolic disorders
Desensitization	Osteonecrosis
Dosing	Pancreatitis
Dyslipidemia	Prophylaxis
Hemorrhage	Thromboembolic
Hepatotoxicity	

Supplement Table 2. PICO(TS) Format
Population
Intervention
Comparator
Outcome
Timeframe
Setting

Supplement Table 3. Categorization of Consensus Statements

Category	Mean score[a]		Outlier[b]
Consensus	≥7.0	and	≤1
Near-consensus	≥6.5	and	≤2
No consensus	<6.5	or	≥3

[a]Mean score = Sum of all Likert scores/Total number of panelists (eg, 1 panelist scored the statement as 5 = 5; 5 panelist scored the statement as 8 = 40; 4 panelist scored the statement as 9 = 36; Mean = (5 + 40 + 36)/10 = 8.1)

[b]Outliers = number of panelists scoring the statement more than 2 Likert points from the mean (eg, Mean = 8.1, 1 panelist scored the statement as 5; Outliers = 1)

Supplement Table 4. Articles used in the Delphi Process
Review articles
Clinical Guidelines, Consensus Statements, Expert Panels
Aldoss I, Douer D. How I treat the toxicities of pegasparaginase in adults with acute lymphoblastic leukemia. *Blood*. 2020;135(13):987-995. doi:10.1182/blood.2019002477
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Lussana F, Minetto P, Ferrara F, Chiaretti S, Specchia G, Bassan R. National Italian Delphi panel consensus: which measures are indicated to minimize pegylated-asparaginase associated toxicity during treatment of adult acute lymphoblastic leukemia? *BMC Cancer*. 2020;20(1):956. doi:10.1186/s12885-020-07461-5
National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia (ALL), Version 1.2022
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. *Leukemia & Lymphoma*. 2011;52(12):2237-2253. doi:10.3109/10428194.2011.596963
van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica*. 2016;101(3):279-285. doi:10.3324/haematol.2015.137380
Systematic Reviews and Meta-analyses
De Stefano V, Za T, Ciminello A, Betti S, Rossi E. Haemostatic alterations induced by treatment with asparaginases and clinical consequences. *Thromb Haemost.* 2015;113(2):247-261. doi:10.1160/TH14-04-0372

Rank CU, Lynggaard LS, Als-Nielsen B, et al. Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia. *Cochrane Database of Syst Rev*. 2020;10(10): CD013399. doi:10.1002/14651858.CD013399.pub2

Clinical studies

Clinical Trials and Prospective studies

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Randomized Clinical Trials

Angiolillo AL, Schore RJ, Devidas M, et al. Pharmacokinetic and pharmacodynamic properties of calaspargase pegol *Escherichia coli* L-asparaginase in the treatment of patients with acute lymphoblastic leukemia: results from Children's Oncology Group Study AALL07P4. *J Clin Oncol.* 2014;32(34):3874-3882. doi:10.1200/JCO.2014.55.5763

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