Asparaginase: The Good, the Bad and the Ugly

Lee Dupuis, RPh, PhD
Paul Gibson, MD, FRCPC
Stephen Sallan, MD

Presentation Description

Asparaginase has long been recognized as a crucial element in the treatment of Pediatric ALL. This interactive panel session will focus primarily on pegaspargase, providing background on its inclusion in ALL therapy, and lessons learned. Cases highlighting the practical challenges of administering this drug and identifying adverse effects will be presented. Furthermore, strategies for continued administration including alternative asparaginase products will be discussed.

Speaker bios

Lee Dupuis, RPh, PhD
Associate Scientist and Clinical Pharmacist
The Hospital for Sick Children, Toronto, ON

Lee has a BSc, BScPhm and MScPhm from the University of Toronto. She completed her pharmacy residency at Sunnybrook Health Sciences Centre and her PhD at the University of Amsterdam. She has held several positions at The Hospital for Sick Children (SickKids) including Coordinator of Drug Information; Manager of Clinical Pharmacy Services, Research & Education; and Clinical Pharmacy Manager – Haematology/Oncology. She is currently an Associate Scientist with the Research Institute, Sick Kids and the Leslie Dan Faculty of Pharmacy, University of Toronto.

Lee's research focuses on the supportive care of children with cancer or undergoing bone marrow transplant with a focus on improving control of chemotherapy-induced nausea and vomiting and creating ways that children can communicate the severity of treatment-related adverse effects. Lee

serves on committees within the Children's Oncology Group, POGO and C17 and on guideline development panels for POGO, American Society of Clinical Oncology, the Dutch Children's Oncology Group and the Multinational Association of Supportive Care in Cancer.

Paul Gibson, MD, FRCPC
Pediatric Oncologist, Children's Hospital, London Health Sciences Centre (LHSC), London, ON
Medical Officer, Pediatric Oncology Group of Ontario
Assistant Professor, Western University, London, ON

Dr. Gibson is a Graduate of Queen's University's Medical School. He completed Pediatric Residency training at B.C. Children's Hospital prior to subspecialty training at The Hospital for Sick Children. He joined the Section of Pediatric Hematology and Oncology at Children's Hospital full time in 2010. He has served as Physician Lead in the LHSC Computerized Provider Order Entry project and is currently a Physician Lead in the PowerChart Oncology project. Dr. Gibson has served as Medical Officer of the Pediatric Oncology Group of Ontario (POGO) since 2015. His role with POGO includes medical support of the POGO Satellite program and a member of the executive oversight committee of the Provincial Pediatric Oncology Planning process.

Stephen Sallan, MD
Chief of Staff, Emeritus
Dana Farber Cancer Institute, Boston, MA

Dr. Stephen E. Sallan is Chief of Staff, Emeritus and the Quick Family Senior Investigator in Pediatric Oncology at Dana-Farber Cancer Institute, and a Professor of Pediatrics at Harvard Medical School.

Dr. Sallan is one of the world's foremost experts on childhood leukemia. His principal contributions include optimizing the use of asparaginase in acute lymphoblastic leukemia (ALL), enhancing outcomes in young adults with ALL, developing "therapeutic windows" for newly diagnosed patients, preventing therapy-related cardiotoxicity, and exploring innovative approaches to the prevention of chemotherapy-induced nausea and vomiting.

After completing his education at Wayne State University in Detroit, he trained in pediatrics at Boston Floating Hospital, Children's Hospital of Philadelphia, and the Hospital for Sick Children, Great Ormond Street, London.

Since 1972, he has pursued his clinical and research career at Boston Children's Hospital and the Dana Farber Cancer Institute.

Overview of PEG-Asparaginase

(DFCI ALL Consortium Experience)

POGO Symposium

Toronto

November 4, 2016

Native E.coli Asparaginase
(<u>not</u> PEG)

- Increases event-free survival in ALL
- Intolerance compromises EFS
- “Silent inactivation” compromises EFS
- Native Erwinia ASP less effective
- Absence of dose:toxicity relationship

PEG-Asparaginase

- Native E.coli asparaginase

  +

  polyethylene glycol linker

- Longer duration in the blood
- (Hoped for) less toxicity

Recent DFCI Randomized Trials

2005 – 2010:

Compared im native E.coli to iv PEG ASP

2012 – 2015:

Compared two types of iv PEG ASP

Asparaginase Randomization 2005-2010

(N = 544)

30 weeks during post-remission therapy

R → PEG ASP 2,500 IU/m2 **IV q 2 weeks**

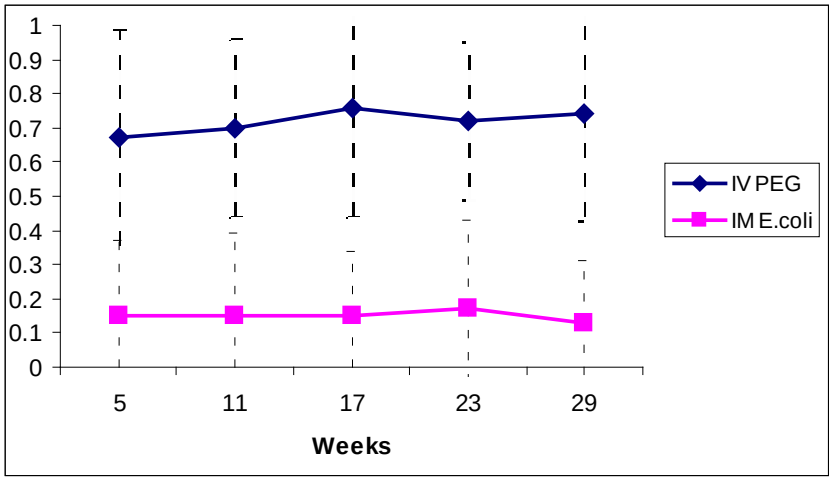
R → E.coli ASP 25,000 IU/m2 **IM q week**

- All patients received IV PEG during remission induction
- PEG ASP – Oncaspar

Place AE et al. Lancet Oncol 16, 2015

IM E. coli versus IV PEG asparaginase

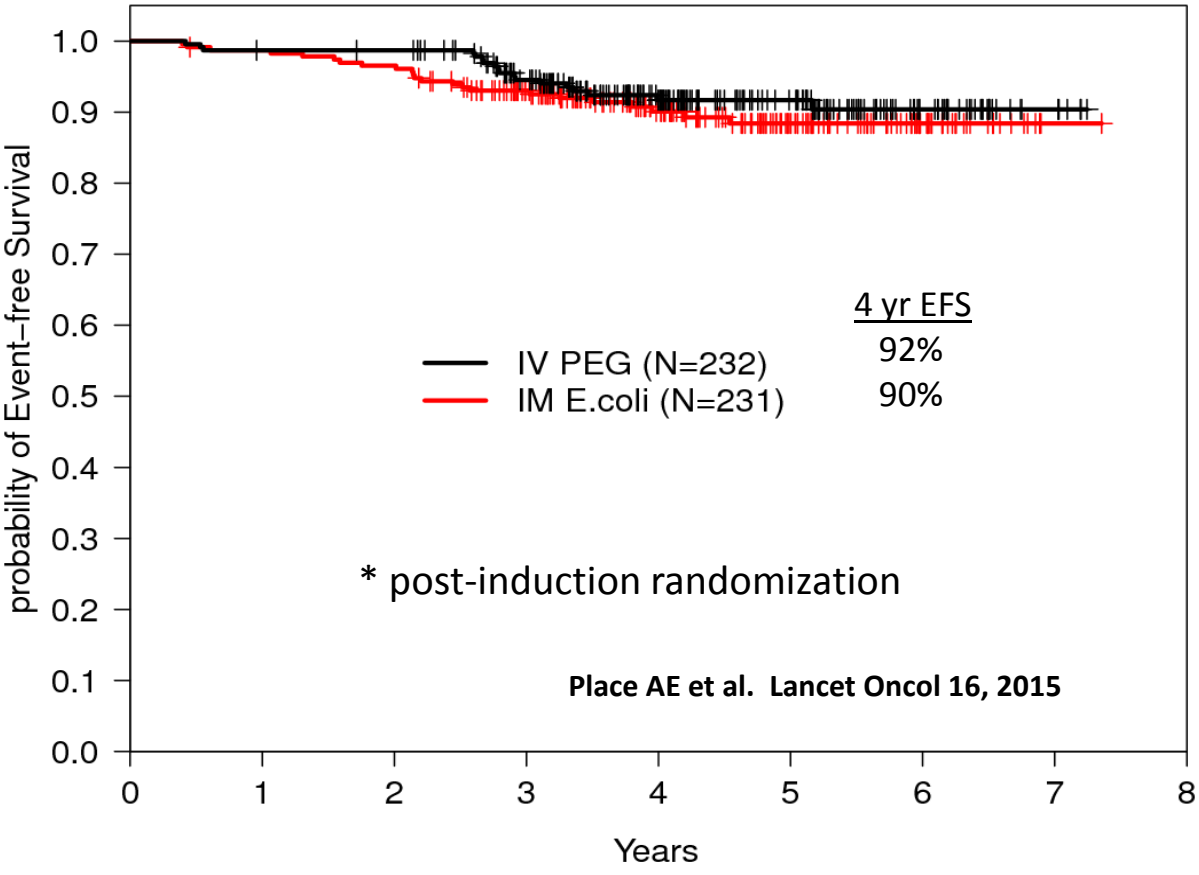
- IV PEG: Median serum nadir ASP 6-7 x higher than E.coli ASP
- % patients with nadir level >0.1 IU/mL
  - IV PEG: 99%
  - IM E.coli: 47%
- Similar toxicities



Conclusions

- IV PEG administration tolerable
- High ASP levels not associated with increased toxicity
- 99% of IV PEG patients have therapeutic ASP levels
  - Very low frequency of silent inactivation
- Outstanding event-free survival

Event-free Survival



Recent DFCI Randomized Trials

2005 – 2010:

Compared im native E.coli to iv PEG ASP

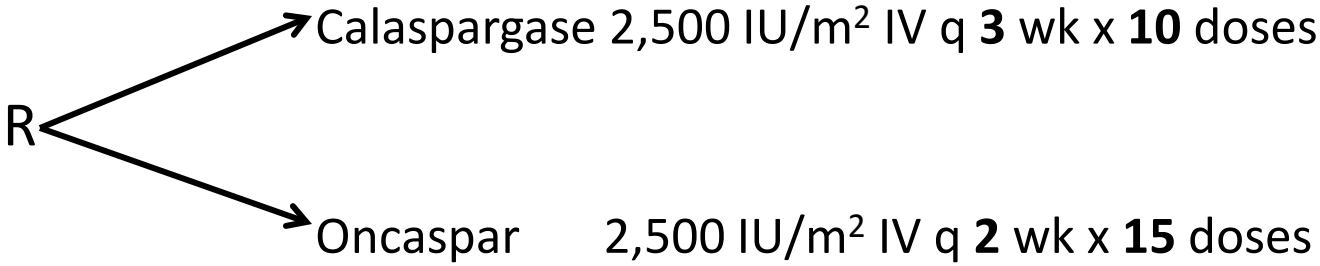
2012 – 2015:

Compared two types of iv PEG ASP

Calaspargase
(aka: SC-PEG)

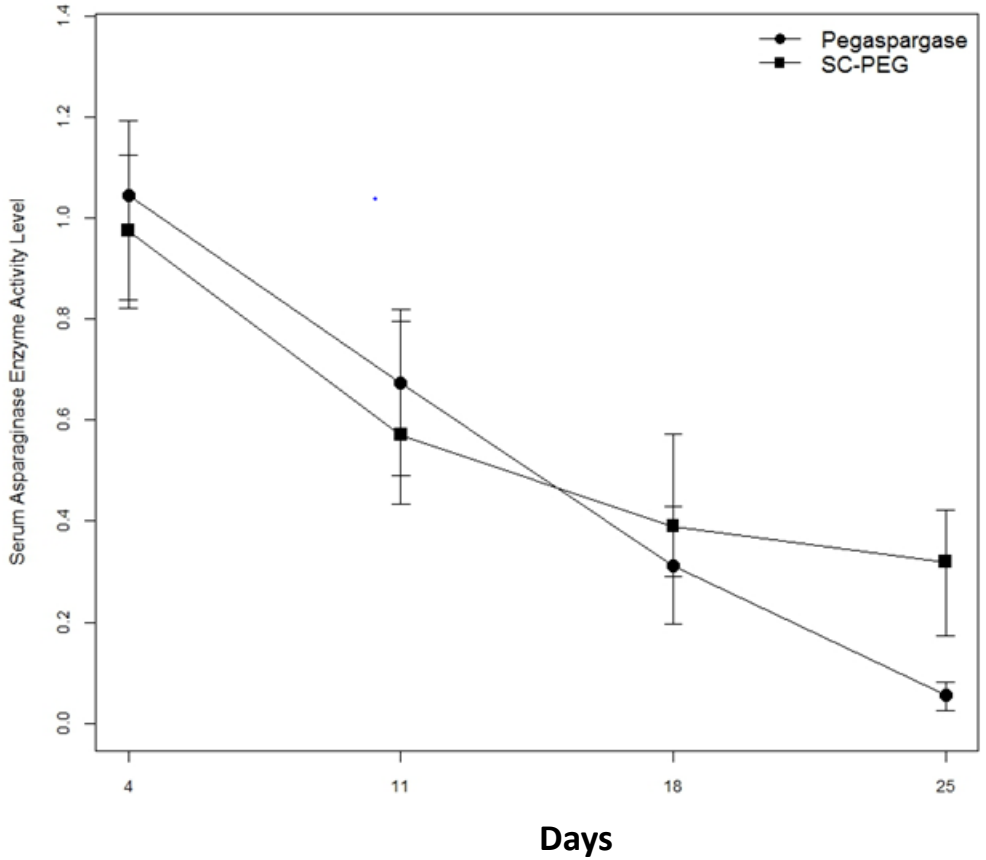
- Like Oncaspar, but a different linker
- Longer duration of asparagine depletion

Asparaginase Randomization (2012 – 2015) N= 239

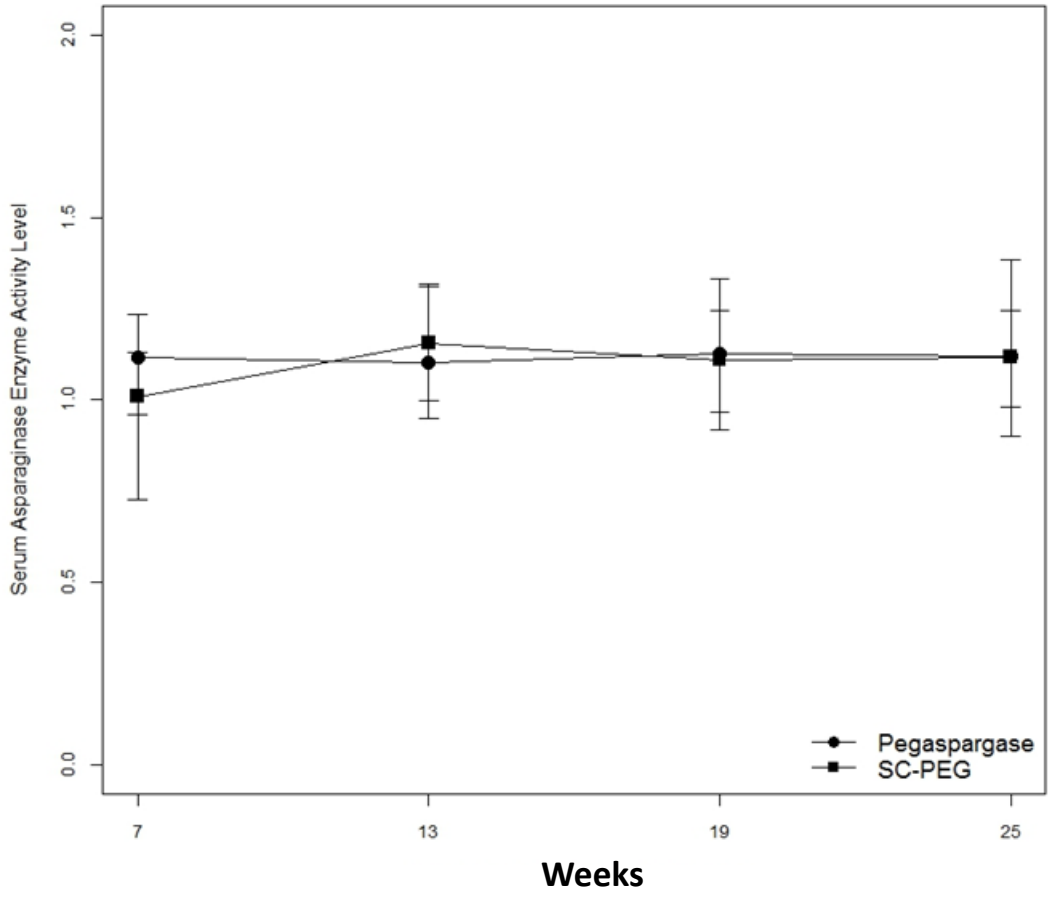


Silverman LB et al. ASH 2016

Serum Asparaginase Activity (SAA) After Single Dose of Drug



SAA During Intensification



Nadir Serum ASP Activity

Wk*	Asparaginase type	% pts with NSAA >=0.1 (IU/mL)
7	Pegaspargase SC-PEG	100 98
13	Pegaspargase SC-PEG	100 100
19	Pegaspargase SC-PEG	100 100
25	Pegaspargase SC-PEG	100 100

Asparaginase Toxicity

Adverse Event	SC-PEG (N=109)	PEG-Asparagase	Oncaspar N = 114		P-value
	N	%	N	%	
Allergy	19	17%	16	14%	**0.58**
Pancreatitis	14	13%	16	14%	**0.85**
Thrombosis	16	15%	13	11%	**0.55**
High bilirubin	20	18%	20	17%	**1.00**
Infection	15	14%	21	18%	**0.37**

A Word On The Adolescents/Young Adults

- Increased hepatic toxicity with PEG
  - Less than with native
- Increased thrombosis with increasing age

Venous Thrombosis by Age

Age (yrs)	VT Rate	p-Value
0-5	2%	
6-10	7%	0.02
11-14	20%	<0.01
15-20	18%	0.01
21-30	25%	<0.01
>30	42%	<0.01

Grace RF et al. Brit J Haemat 2011

Conclusions

- Accepted “Knowns” –
  - PEG ASP is effective
  - IV route enhances QOL
  - With “continuous” schedule:
    - High drug levels
    - Rare “silent inactivation”
    - Drug monitoring unnecessary
  - With “discontinuous” schedule native ASP
    - Variable levels
    - ~10% silent inactivation
    - Drug monitoring recommended

Conclusions

- Remaining “Unknowns” –
  - Optimal duration asparagine depletion?
- With “discontinuous” IV PEG ASP
  - Incidence of silent inactivation?
- Most favorable PEG ASP preparation?
- Why age-related toxicities?

Asaparaginase in ALL

- Here for foreseeable future
- Know how to use it!

Asparaginase: the BAD . . . . the UGLY . . . .

Lee Dupuis RPh, PhD

Paul Gibson, MD

POGO Symposium

November 4, 2016

UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY
SickKids
Children's Hospital
London Health Sciences Centre
Schulich
MEDICINE & DENTISTRY

Leukemia
POGO Successes • Advances • Challenges
PEDIATRIC ONCOLOGY GROUP OF ONTARIO 2016 Multi-Disciplinary Symposium on Childhood Cancer • November 4-5, 2016 • Westin Prince Hotel, Toronto

Asparaginase:
A LOT of Potential 'Bad and Ugly'

- Thrombosis/Hemorrhage
- Pancreatitis
- Hyperglycemia
- Allergy

Hypersensitivity reactions: clinically **apparent**

- Pegaspargase IV (23.5%) vs IM(8.7%)
- 90% with second or subsequent dose
- Patients treated as per HR protocols at highest risk
- Most associated with sub-therapeutic asparaginase activity

Hasan et al. Pediatr Blood Cancer 2016

Hypersensitivity reactions: clinically **silent**

- Sub-therapeutic asparaginase activity without clinical signs of allergy
- Incidence: E coli asparaginase: ~10%

Vrooman et al. Blood 2013

Clinically Silent: The Danger of not knowing!

Groups	Clinical Allergy	Ab(+)	Number (%) of Patients	Events (30 mo)	Hazard Ratio	
					Observed	Expected
A	No	No	57 (20%)	3/57	1.0	0.66
B*	Yes	No	27 (10%)	2/27	1.3	0.86
C*	Yes	Yes	115 (41%)	3/115	0.6	0.38
D**	No	Yes	81 (29%)	13/81	3.2***	2.11
Total			280 (100%)	21/280		

*Patients were treated with *Erwinia* ASNase after the clinical allergy symptoms appeared.
**Silent hypersensitivity patients. These patients had the highest hazard ratio, which was statistically significant over the other groups of patients.
***Log rank $P = 0.01$.

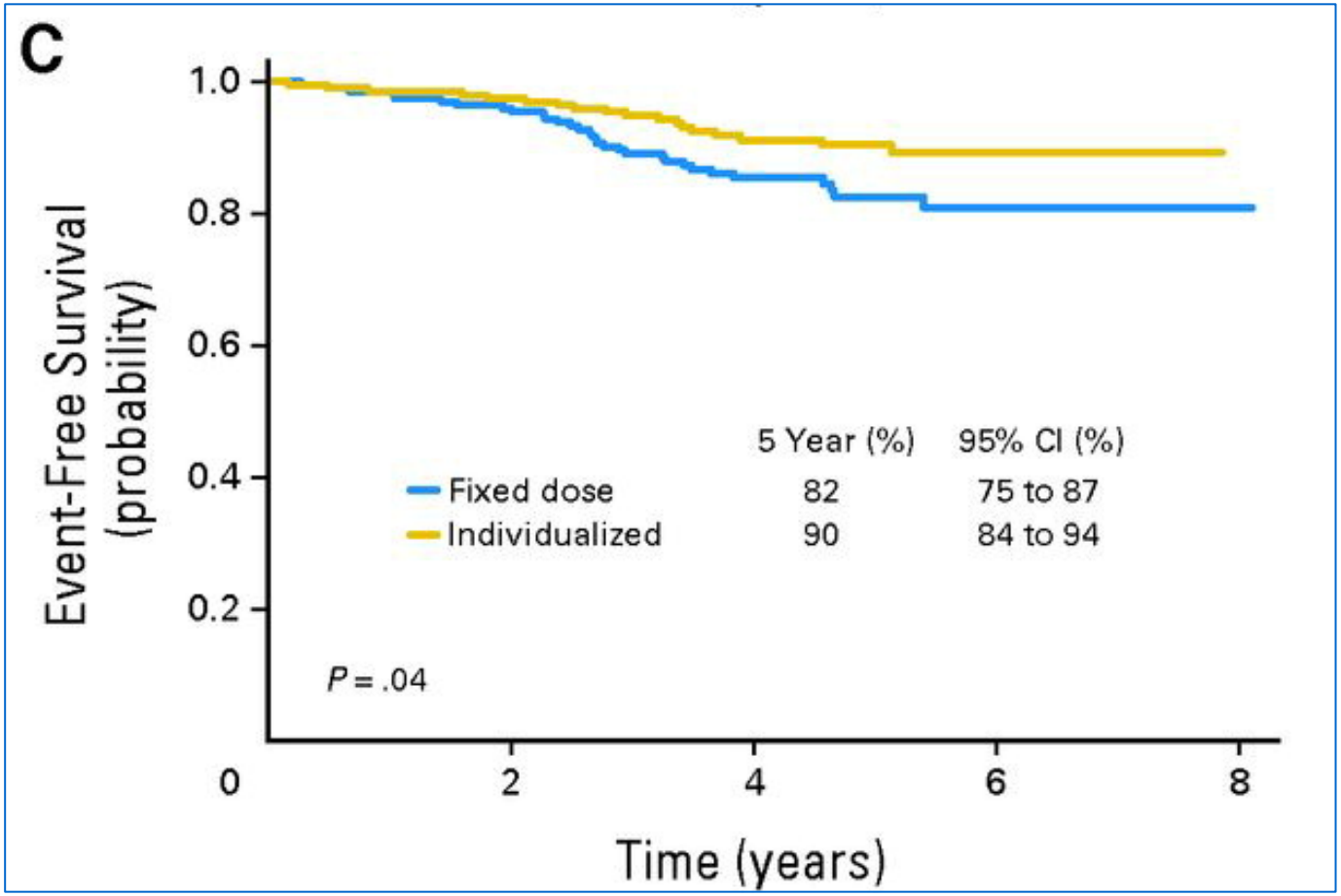
Panosyan et al, *JPHO*, 2004

Asparaginase Activity

- Sustained depletion of asparagine required for effective treatment
- Asparaginase activity threshold ≥ 100 IU/L

  (0.1 IU/mL)
  - pegaspargase: at day 6 or 7 post dose
  - Erwinia asparaginase: at 48 hours post dose
  - E.coli asparaginase: at 72 hours post dose (twice weekly dosing)

Asparaginase Activity Monitoring: DFCI



On to the Patients… the BAD . . . .

- JM 14 year old boy with T Cell ALL: Day 4 induction
  - receives platelets prior to planned line placement
  - pegaspargase 4,170 IU IV over 90 minutes
  - ondansetron IV pre-pegaspargase
  - at end of infusion:
    - 2 hives on left cheek
    - diphenhydramine given
- Plan for next dose on Day 18?

Evaluation Allergic Reactions

- Moderate allergic reaction
  - resolves quickly and completely without epinephrine and
  - involves either the skin-mucosal or GI system (e.g. crampy abdominal pain, vomiting or diarrhea) but not both

Cheng A. Paediatr Child Health 2011;16:35

What is the Plan for next dose on Day 18?

A. Give pegaspargase as per road map
B. Give pegaspargase with ondansetron, hydrocortisone, ranitidine and diphenhydramine as pre-medications
C. Switch to Erwinia asparaginase
D. Decide based on Day 11 asparaginase activity result

On to Day 11 for JM…

- Asparaginase activity = 1.3 IU/mL

Allergic-Like Reactions

- AKA ‘pseudoallergic reactions’
- Not necessarily immune-mediated
- Possible precipitants of allergy-like reactions:
  - polyethylene glycol
  - concomitant drug, blood product, food
  - rapid increase in plasma ammonia concentrations
- Allergy-like reactions to asparaginase
  - occur earlier than allergic reactions where asparaginase activity is sub-therapeutic
  - future doses may be given with/without pre-medication

Kloos et al PBC 2016: 63: 1928

So about day 18…

A. Give pegaspargase as per road map
B. Give pegaspargase with ondansetron, hydrocortisone, ranitidine and diphenhydramine as pre-medications
C. Switch to Erwinia asparaginase

And now.. the UGLY . . . .

- BT 17 year old boy with High Risk pre-B ALL
- Day 15 Consolidation
  - pegaspargase 5,000 IU IV over 90 minutes: Well Tolerated
- Day 22
  - asparaginase activity = 0.04 IU/mL
- Plan for next dose on Day 43?

What's Next?

A. Give pegaspargase on Day 43 as per road map
B. Make up Day 15 asparaginase dose by starting Erwinia asparaginase as soon as Day 22 asparaginase activity result known
C. Starting on Day 43, give Erwinia asparaginase instead of pegaspargase
D. B and C

Back to the Patient..

- BT is now at Day 4 of Delayed Intensification
  - Erwinia asparaginase IV Q MWF x 6 doses
  - asparaginase activity on Day 8 = 0.04 IU/mL
- Plan for next doses on Day 18?

the UGLY . . . .

Plan for next doses on Day 18?

A. No more asparaginase to be given
B. Increase the Erwinia asparaginase dose
C. Give Erwinia asparaginase Q48H rather than Q MWF
D. Give Erwinia asparaginase IM rather than IV

Routine Asparaginase Activity Monitoring

- Consider adopting asparaginase activity monitoring as standard of care
- Challenges
  - Extra clinic visits required for bloodwork
  - Contingency plan may be needed for weekend bloodwork
  - Educate parents & patients about significance of result
  - Allow for lag time between sending sample to outside lab and obtaining result

Routine Asparaginase Activity Monitoring: Why NOT??

- Must be cautious applying lessons learned form DFCI protocol with 30 weeks of intensive asparaginase to other (i.e. COG/BFM-based therapy)

Protocol	Doses of Pegaspargase
DFCI	16
COG SR pre-B	2
COG HR pre-B	7

Asparaginase Activity Threshold?

- What Level?
  - Traditionally ≥ 100 IU/mL
  - **HOWEVER**
    - AALL 07P4: 51 patients receiving pegaspargase 2500 IU/m^2 IV
    - all patients with asparaginase activity >0.02 IU/mL had an undetectable plasma asparagine concentration
    - “the threshold level of serum asparaginase activity needed for serum asparagine depletion is 0.02 IU/mL rather than 0.1 or 0.4 IU/mL as previously published.”

Schore et al. J Clin Oncol 34, 2016 (suppl; abstr 10508)

Questions???

Selected References

- Van der Sluis IM et al. Haematologica 2016; 101(3): 279-85.
- Tong WH et al . Haematologica 2013; 98(5): 753-9.
- Tong WH et al. Blood 2014; 123 (13): 2016-33.
- Hasan H et al. Pediatr Blood Cancer 2016; doi: 10.1002/pbc.26200