Evaluation of the emetogenicity of intravenous erwinia asparaginase at a tertiary teaching hospital's oncology centre

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Background

- Erwinia asparaginase (EA) is a chemotherapy medication for the treatment of patients with Acute Lymphoblastic Leukaemia (ALL) who have previously had a hypersensitivity reaction to E. coli-derived asparaginase[1]
- In initial clinical trials it was only administered by intramuscular (IM) injection[2]
- More recent clinical trials have shown it to be safe and efficacious when administered via the intravenous (IV) route and was approved by the Food and Drug Administration for IV use in 2014[2]
- Anecdotally, it appeared there was a significant incidence of nausea and vomiting from IV EA
- Chemotherapy induced nausea and vomiting is a common and debilitating side effect of chemotherapy and adversely affects the quality of life of patients being treated for cancer[2,3,4]
- Chemotherapy induced nausea and vomiting is categorised as acute, delayed and/or anticipatory in nature
- Emetogenic risk is classified into four groups as per the MASCC/ESMO antiemetic guideline; high (emetic risk >90%), moderate (30-90%), low (10-30%) and minimal (<10%)[5]
- There has been little published information regarding the emetogenic risk of EA[2] and it is not included in recent international antiemetic guidelines[3,5]
- There is currently no consensus on the prescribing of antiemetics to prevent EA induced nausea and vomiting.

Aim

- To assess the incidence of nausea and vomiting in paediatric patients receiving intravenous erwinia asparaginase.

Methods

- A retrospective case-note audit conducted at a tertiary paediatric hospital (Department of Haematology & Oncology, Women's and Children's Hospital, South Australia)
- Patients who received IV EA from 2012 to 2017 were identified from the pharmacy chemotherapy batch book
- Data was collected from the chemotherapy batch book and the patient's case notes.
- The patient's first course (up to 7 doses) of EA was included for analysis.

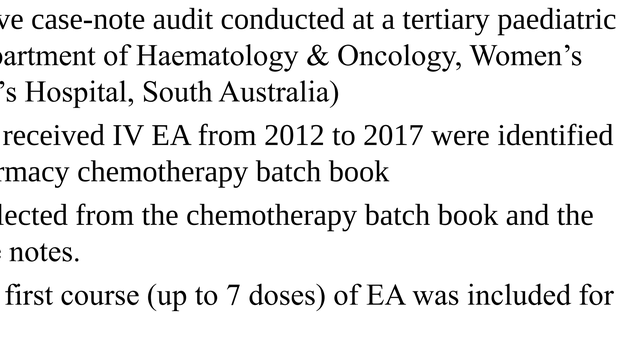
Results

Patient demographics

- 14 patients were included for analysis
  - 64% males and 36% females
- The median age was 5.5 years (range: 11 months – 16 years).

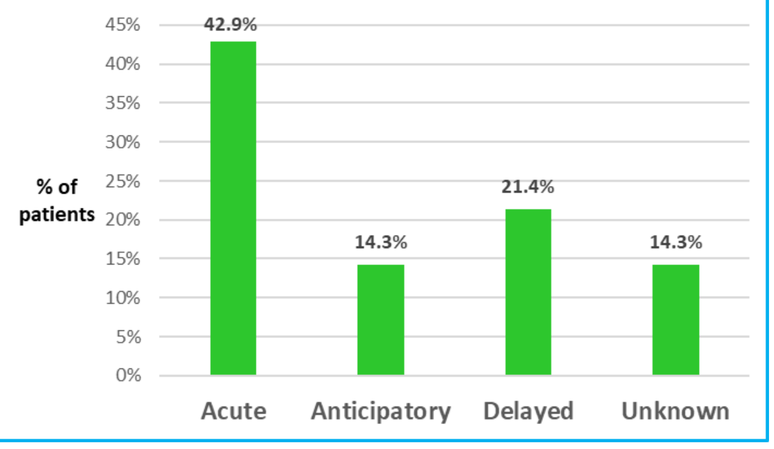
Incidence and impact of nausea and vomiting

FIGURE 1: OCCURENCE OF VOMITING FROM AT LEAST 1 DOSE OF ERWINIA ASPARAGINASE



- 4 patients had nausea without vomiting from at least 1 dose of EA
- 22% of total doses of EA resulted in a vomit (total doses = 76)
- EA did not contribute to or prolong hospital stay in any patients.

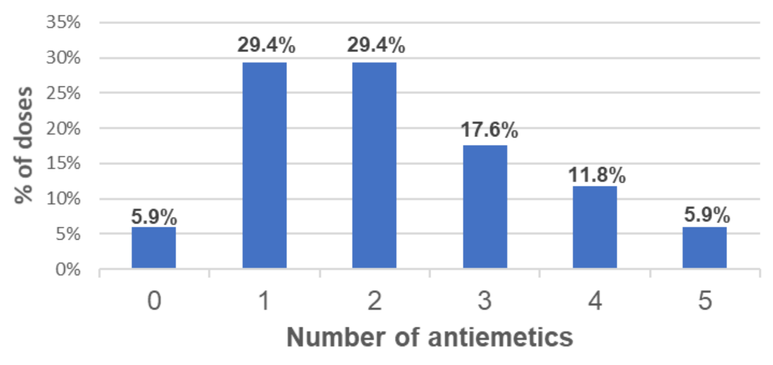
FIGURE 2: TYPE OF VOMITING



Antiemetics

- Ondansetron was administered for 94% of doses that resulted in vomiting
- More than 1 antiemetic was administered for 26% of total doses of EA.

FIGURE 3: NUMBER OF ANTIEMETICS ADMINISTERED FOR DOSES ASSOCIATED WITH VOMITING



Impact of infusion time

- EA was administered over 1 hour for every dose for 12 patients, 2 hours for every dose for 1 patient and over 1 to 2 hours for 1 patient
- There was no correlation between infusion time and emetogenic risk.

Impact of dose

- 4 patient received each dose of EA at 25,000units/m^2 and 10 patient received each dose of EA at 20,000units/m^2
- There was no correlation between dose and emetogenic risk.

Impact of other chemotherapeutic agents

- There was no correlation between emetogenic risk and other chemotherapy medications administered within 48 hours of EA.

TABLE 1:

			NUMBER OF ERWINIA ASPARAGINASE DOSES				
PATIENT NUMBER	SEX	AGE	TOTAL	VOMITING	NAUSEA (NO VOMITING)	ANTIEMETICS	ANTIEMETICS GIVEN
1	M	4	6	1	0	5	O, M
2	F	5	6	3	2	6	O, M, C, L, Dr
3	F	11	6	4	1	6	O, M, A, C, L
4	M	12	3	2	0	2	O, M
5	M	11	6	1	2	4	O, M
6	F	5	7	1	0	2	O, D
7	F	16	7	0	0	0	
8	M	6	7	4	1	6	O, M, L
9	M	3	7	0	0	3	O
10	M	16	2	0	0	0	
11	M	5	7	1	0	3	O
12	M	11 months	3	0	0	0	
13	M	10	2	0	0	1	O, L
14	F	5	7	0	0	3	O

O = ondansetron
M = metoclopramide
C = cyclizine
L = lorazepam
Dr = droperidol
A = aprepitant
D = dexamethasone

Discussion

- Up to 30% of patients who receive the *Escherichia coli*–derived product will develop an allergy, which necessitates a switch to the antigenically distinct *Erwinia*-derived asparaginase[2]
- All children at the WCH now receive EA via the IV route since this option was accepted by international study consortiums (e.g. Children's Oncology Group) as it is associated with less discomfort and associated patient distress compared with intramuscular injection
- In a paediatric oncology guideline published in 2011, asparaginases were classified as minimally emetogenic, however, the available forms were not differentiated regarding their emetogenicity. EA was only administered via the IM route at the time of publication[4]
- In a pharmacokinetic study of IV EA in 30 patients (1 to 30 years of age), the reported incidence of vomiting was 20%, despite premedication with ondansetron[1]
- The results from this study indicate that vomiting is common amongst patients who receive EA and more than 1 antiemetic may be necessary to prevent/treat vomiting
- In this study, 57% of patients had documented vomiting from at least 1 of their doses, suggesting that EA should be classified at least as moderately emetogenic as per the MASCC/ESMO antiemetic guidelines.

Limitations

- Small sample size from single centre
- Retrospective case-note audit contributing to limitations in data collection including:
  - Lack of clarity around whether antiemetics were given pre or post the administration of EA and pre or post reports of nausea and vomiting
  - Difficulty distinguishing between acute and delayed nausea and vomiting based on case note records
  - Reliance on reporting of nausea and/or vomiting from patients/their families and documentation from health care professionals.

Future Directions

- Review the incidence of nausea and vomiting with the administration of EA via the IM route and compare with the IV route
- Review the incidence of nausea and vomiting with EA in paediatric patients interstate
- Incorporate the emetogenic risk of EA into antiemetic guidelines.

Conclusion

- In this study, 57% of patients experienced vomiting from at least 1 dose of EA. This suggests that EA should be classified as at least moderately emetogenic
- Further studies are necessary to increase the validity of these results before EA can be included in antiemetic guidelines.

References

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4. Dupuis LL et al. 'Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients'. Pediatr Blood Cancer. 2013;60(7):1073–82
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