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SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

Fixed Dose 7.5mg Rasburicase is safe and cost-effective in preventing tumour lysis syndrome (TLS) in adult haematology patients at University College Hospital, London

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Conflict of Interest Disclosure

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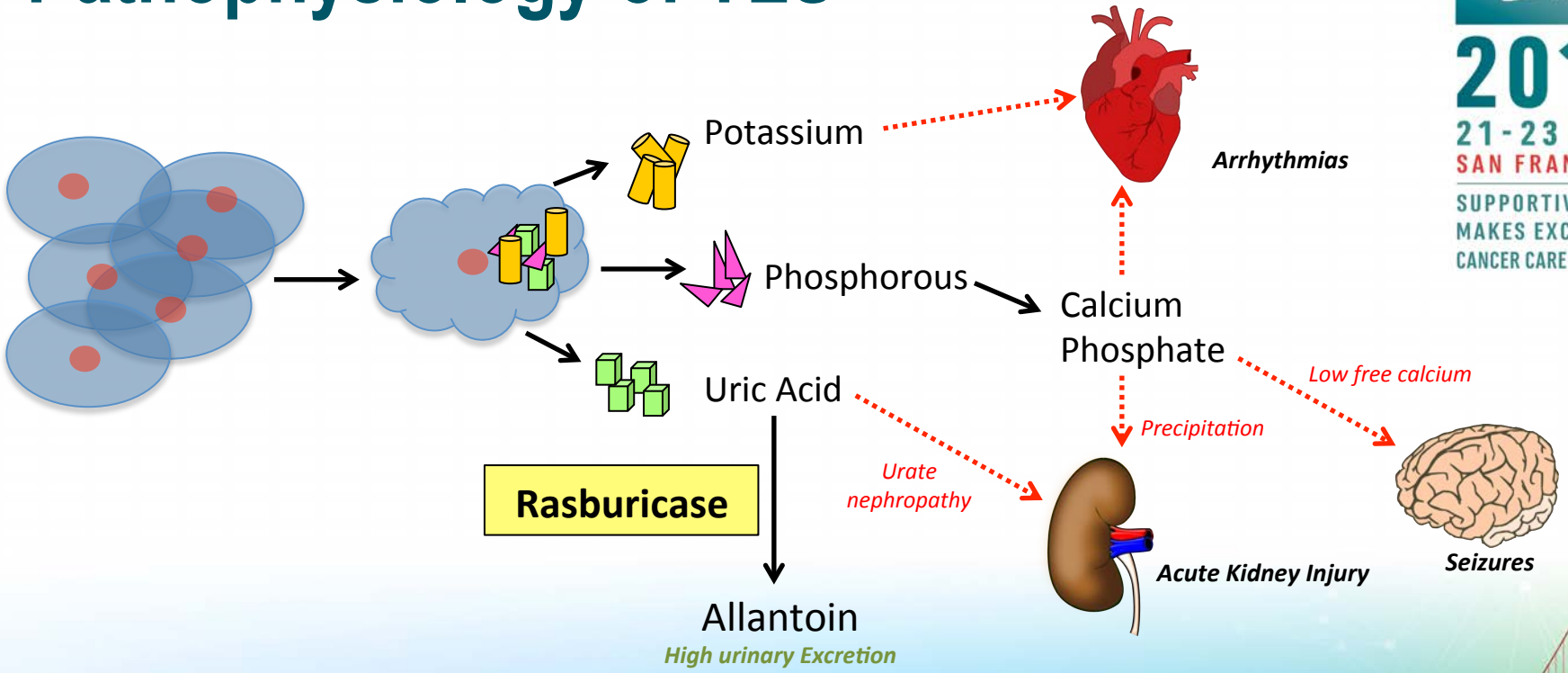
Has no real or apparent conflicts of interest to report.

Background

- Haematological malignancies with a high tumour burden and/or cell turnover are at risk of tumour lysis syndrome (TLS); this is an oncological emergency
- Rasburicase, a DNA recombinant urate oxidase, is recommended as prophylaxis in those patients at high risk of TLS development
- Licensed dose of Rasburicase is 200mcg/kg
- UCLH guidelines suggest the use of Rasburicase 7.5mg fixed dose in adult haematology patients

Pathophysiology of TLS



Rationale

- In 2015, UCLH amended their TLS prophylaxis guidelines to recommend a fixed dose of 7.5mg, based on British of Haematology (BSH) guidelines[1]

- Current UCLH guidelines suggest using Rasburicase prophylaxis 7.5mg for up to 3 days for patients stratified as high risk

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[1] Jones et *al*, 2015. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Hematology, British Journal of Haematology. 169, 661-671

Defining High Risk

- Baseline risk according to disease subtype
- Renal dysfunction GFR <60ml/min or renal infiltration
- Abnormal bloods = 2+ raised
  1. *Urate≥ULN*
  2. *K+ ≥ 6.0mmol/L*
  3. *PO4- ≥ 1.45mmol/L*

Disease subtype	COLUMN A Baseline risk	COLUMN B If elevated uric acid, K+ or PO4 levels	COLUMN C If renal dysfunction
Multiple myeloma / Myeloproliferative neoplasms / Hodgkin and Indolent Non-Hodgkin lymphoma			
All patients and sub-types	Low	Low	Intermediate*
Chronic Myeloid Leukaemia			
Chronic phase	Low	Low	Intermediate
Blast crisis	see below	see below	see below
Chronic Lymphocytic Leukaemia			
Treatment with alkylating agents	Low	Low	Intermediate*
Venetoclax – All lymph nodes<5cm AND ALC<25x10^9/L	Low	Low	Intermediate
Venetoclax – Any lymph node 5-10cm OR ALC≥25x10^9/L	Low	Intermediate	Intermediate
Venetoclax – Any lymph node ≥10cm **OR** ALC≥25x10^9/L AND any lymph node ≥5cm	High	High	High
Acute Myeloid Leukaemia or Chronic Myeloid Leukaemia blast crisis			
WBC <25x10^9/L with LDH <2xULN	Low	Low	Intermediate
WBC <25x10^9/L with LDH ≥2xULN	Intermediate	High	High
WBC ≥25x10^9/L and <100x10^9/L	Intermediate	High	High
WBC ≥100x10^9/L	High	High	High
Acute Lymphoblastic Leukaemia			
WBC <100x10^9/L with LDH <2xULN	Intermediate	High	High
WBC <100x10^9/L with LDH ≥2xULN	High	High	High
WBC ≥100x10^9/L	High	High	High
Burkitt Leukaemia			
All patients	High	High	High
Burkitt Lymphoma			
Stage 1-2 with LDH <2xULN	Intermediate	Intermediate	High
Stage 1-2 with LDH ≥2xULN	High	High	High
Stage 3-4	High	High	High
Aggressive Non-Hodgkin lymphoma			
All patients with LDH <ULN	Low	Low	Intermediate*
Non-bulky disease with LDH ≥ULN	Intermediate	High	High
Bulky disease with LDH ≥ULN	High	High	High

Risk stratification of TLS according to haematological malignancy and laboratory values

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Objective

- To assess the efficacy of Rasburicase 7.5mg fixed dose in the prevention of TLS in high risk adult haematology patients
- To analyse the potential cost saving using fixed 7.5mg dose over the licensed dose of 200mcg/kg

Method

- Retrospective audit of high risk adult haematology patients who had received 7.5mg Rasburicase prophylaxis
- 12 month period from 1st April 2017 to 30th April 2018
- Patients identified using electronic records
- Prescribing software and notes used to confirm diagnosis, Rasburicase indication (prophylaxis vs treatment) and chemotherapy received
- Patients reviewed for subsequent development of TLS
- Cost of fixed dose Rasburicase was compared to the licensed dose

Exclusion Criteria

- The following were excluded from the audit:

  (1) Patients on Intensive care unit and outlying wards

  (2) Doses that were prescribed but never given

  (3) Patients given a dose of Rasburicase more than 3 days before chemotherapy was started

Results

- Fixed dose Rasburicase was administered to 57 high risk patients

Patient details who received Rasburicase fixed dose 7.5mg prophylaxis and cost-analysis at UCLH over a 12 month period.	
Patient demographics	n=57
Sex: Male, n (%)	36 (63%)
Age in years, median [range]	55 [20-83]
Weight in kg, median [range]	80 [48.5-143]
Diagnosis, n (%)	
Aggressive Non-Hodgkin Lymphoma (NHL)	14 (24.5)
Burkitts Lymphoma	5 (8.8)
Acute Myeloid Leukaemia (AML)	18 (31.6)
Acute Lymphoblastic Leukaemia (ALL)	9 (15.8)
Chronic Lymphocytic Leukaemia (CLL)*	11 (19.3)
Rasburicase fixed dose 7.5mg usage	
Total number of fixed doses administered	108
Fixed dose 7.5mg administered, median [range]	1 [1-6]
*Venetoclax treatment with high tumour burden of lymph node >10cm and/or renal impairment	

Results

- Only 3 out of 57 patients (5.3%) developed TLS

Table 2: Incidence of tumour lysis syndrome (TLS) in patients who received Rasburicase 7.5mg fixed dose at UCLH over a 12 month period

	Patient 1	Patient 2	Patient 3
Diagnosis	AML	Burkitts lymphoma	Aggressive NHL
Number of prophylactic fixed dose 7.5mg given	4	2	1
Laboratory TLS[1] occurred	Yes	Yes	Yes
Clinical TLS[2] occurred	No	Yes	Yes
Number of treatment dose 200microgram/kg/day Rasburicase given	2	2	3

[1]Defined as abnormal serum values of 2 or more (uric acid, potassium, phosphate, albumin-adjusted calcium) either at presentation or change by 25% within 3 days before or 7 days after chemotherapy

[2]Defined as laboratory evidence of TLS plus 1 or more of the following: serum creatinine >1.5xULN; cardiac arrhythmia or sudden death; seizure

Patient 1 - AB, 22y old male: AML

- Fla-IDA started on 03.03.18
- 4 prophylactic 7.5mg doses given, 2 treatment doses given (*)
- Developed laboratory TLS, No clinical TLS symptoms, Cr stable

	Pre-chemotherapy bloods		TLS bloods			Normalizing bloods	
	03.03.18	04.03.18	05.03.18*	06.03.18*	07.03.18	08.03.18	09.03.18
K^+	3.5	3.7	4.6	5.1	4.2	4.3	3.7
PO_4^-	1.01	1.24	1.64	1.87	1.33	1.26	1.25
Cr	63	68	54	52	43	55	50
Adj $Ca2^+$	2.25	2.21	2.19	2.12	1.96	2.27	2.36

- K^+ and $PO4^-$ normalized at 72hours
- Alive

Patient 2 – SB, 50y old male: Burkitt's Lymphoma

- R-CODOX-M started on 26.01.18
- 2 prophylactic 7.5mg doses given, 2 treatment doses given (*)
- Developed laboratory TLS
- Development of clinical TLS symptoms: rising Cr and abnormal ECG

	Pre-chemotherapy bloods	TLS bloods			Normalizing bloods	
	26.01.18	27.01.18 *	28.01.18 *	29.01.18	30.01.18	31.01.18
K^+	3.6	4.8	4.6	4.3	3.6	3.9
PO_4^-	1.0	1.74	2.21	1.14	0.78	0.72
Cr	73	81	94	64	60	50
Adj $Ca2^+$	2.47	2.32	2.24	2.28	2.32	2.24

- K^+ and $PO4^-$ normalized at 48-72 hours
- Alive

Patient 3 – AT, 75y old male: Aggressive NHL

- Pixantrone started on 13.07.17
- 1 prophylactic 7.5mg dose given, 3 treatment doses given
- Developed laboratory TLS
- Development of clinical TLS symptoms: rising Cr, abnormal ECG

	Pre-chemotherapy bloods		TLS bloods			Normalizing bloods	
	13.07.17	14.07.17	15.07.17	16.07.17	17.07.17	19.07.17	20.07.17
K^+	4.3	4.4	5.4	5.7	5.0	4.6	4.1
PO_4^-	0.57	0.60	0.94	1.32	1.57	1.17	1.04
Cr	96	99	132	168	169	143	121
Adj $Ca2^+$	2.35	2.34	2.12	1.96	2.04	2.34	2.35

- K^+, $PO4^-$ and Cr normalized at 96hours
- Alive

Results

- Over 12 months, using a Rasburicase 7.5mg fixed dose in high risk patients resulted in a 54% cost saving compared to the licensed dose

Potential annual spend using 200microgram/kg dosing
£114,330

Annual cost saving
£61,816

Actual annual spend using fixed 7.5mg dosing
£52,514

Discussion

- A meta-analysis[2] of adults who received Rasburicase prophylaxis reported 7.4% of patients (n=768) developed clinical TLS
- Only 5.3% of high risk patients who received a fixed flat dose of 7.5mg developed TLS (3.5% clinical TLS)
- Median doses of treatment 200mcg/kg needed = 1
- Similar incidence of TLS in our institution to reported literature – suggests no increase in incidence of TLS using 7.5mg dosing
- Using fixed dose Rasburicase has shown significant cost savings compared to the licensed dose

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[2] Lopez-Olivio et *al*, 2013. Rasburicase in tumour lysis syndrome of the adult: a systematic review and meta analysis, AM J Kidney Dis. 62(3) 481-492

Conclusion

Fixed dose 7.5mg Rasburicase prophylaxis in high risk adult haematology patients appears to be safe and cost effective

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Limitations

- Patients starting prophylactic Rasburicase in ICU

  Not captured by the initial report of dispensing data

- Uric acid levels

  Not analysed at UCLH; urate levels used as a surrogate for TLS monitoring

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Questions?