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Incidence and management of PEGylated-asparaginase related thrombosis in adults with ALL

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INTRODUCTION

Asparaginase is a cornerstone of acute lymphoblastic leukaemia (ALL) therapy; however its use is associated with a number of toxicities including increased risk of thrombosis. There is considerable uncertainty about the frequency of asparaginase-related thrombosis in adult ALL, with reported incidences ranging from 1%-36%. Whilst there are guidelines for the paediatric population, there are no specific adult guidelines on the prevention and management of venous thromboembolism (VTE) prevention in adult ALL.

AIM

In adult ALL patients being treated with regimes including asparaginase we aim to:

- Assess the frequency and anatomical location of asparaginase-induced thrombosis
- Record the management of thrombotic episodes, including measurement of antithrombin, liaison with RLH haemostasis team, choice of anticoagulant and usage of antithrombin concentrate.
- Investigate factors associated with increased risk of asparaginase (such as increased BMI)
- Assess whether asparaginase was reintroduced after a first thrombotic event, and the rate of further thrombosis if this was done.
- Record the rate of hypertriglyceridaemia and pancreatitis

Population:
We will look at all adult patients treated with asparaginase for ALL since 2014 at St Barts Hospital, using a list identified by pharmacy. This time point reflects the UKALL protocol change that reduced the asparaginase dosing from late-2013 onwards [Patel, 2017].

METHOD

We retrospectively analysed 33 consecutive adult patients treated with PEGylated asparaginase (PEG-ASP) as part of the UKALL14 regime from 2014 – 2019 at St Bartholomew's Hospital. The protocol specifies one (age ≥40years) or two doses (age <40years) of 1000 IU/m^2 PEG-ASP during standard phase 1 induction. Clinical notes and imaging were used to determine the frequency of thrombotic events during Phase 1 and 2 induction therapy incorporating PEG-ASP, the choice of anticoagulation strategy, and the use of antithrombin (AT) concentrate.

RESULTS

Of the 33 patients (13F, 20M – age range 23-60, mean 39.8) who received PEG-ASP, there were 14 symptomatic thrombotic events in ten patients (30%, 5F,5M, mean age 40.7). Of these 14 events, 3 occurred prior to PEG-ASP being given. The majority were deep vein thromboses (DVT) (64%). There were 2 superficial vein thromboses (SVT) (14%), 1 internal jugular vein thrombosis, 1 pulmonary embolism (PE) and 1 episode of sagittal sinus venous thrombosis with cortical vein thrombosis. All patients were treated with therapeutic low molecular weight heparin (LMWH) with five patients (50%) having antithrombin (AT) levels checked, all of which were below the normal range (see table 1). Two patients received AT concentrate and five had further asparaginase after the thrombotic event with two patients still awaiting further treatment. Three events were PICC line associated.

Table 1

Age and Gender	Thrombosis Site	Days since last dose of PEG-ASP administered	Antithrombin level at time of thrombosis (normal range 81-119 IU/dl)
31M	L upper DVT	10	35
	R upper DVT	11	35
	R lower DVT	8	33*
	Bilateral upper DVT	24	65*
30F	Cerebral venous sinus thrombosis	13	27*
26M	Internal jugular vein thrombosis	Pre Asparaginase	40
	PE	3	Not re-tested
52F	L upper DVT	5	Not measured
31M	L upper DVT	Pre Asparaginase	Not measured
31M	L lower DVT	27	41**
47F	L lower DVT	17	Not measured
59F	R lower SVT	Pre Asparaginase	42
47F	R upper DVT	60	Not measured
53M	R upper SVT	21	Not measured

*Antithrombin concentrate used
**Checked 3 months after thrombosis diagnosed

DISCUSSION

Our single-centre data demonstrate a high penetrance of venous thrombosis of varying severity, with a predominance of DVT site. Despite demonstration of low antithrombin levels, there was significant variation in replacement therapy. Our data shows a similar mean age in those with and without thromboses which differs from previous data [Grace, 2011] – although age over 30 was identified as being high risk in previous studies. Unfortunately, data were not reliably available on other thrombotic risk factors such as BMI and smoking status. Further data on the impact of antithrombin concentrate and risks of re-exposure to asparaginase are necessary.

Recent guidance by Zwicker et al[4] since abstract publication has been published for management of asparaginase induced thromboses going some way to define guidance in adults.

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