Determining the outcomes from pegfilgrastim use in adult acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL)

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Background

Acute leukaemia is a rare and aggressive cancer of the white blood cells that is fatal if left untreated. The haematological malignancy affects the myeloid (acute myeloid leukaemia [AML]) or lymphoid (acute lymphoblastic leukaemia [ALL]) cells and treatment often involves intense chemotherapy, resulting in prolonged periods of immunosuppression that can leave patients at high risk of infections.[1] Almost all patients undergoing treatment experience grade 4 neutropenia (neutrophils <0.5x10^9/L).[1] The risk of infection increases in direct proportion with the duration of neutropenia. Mortality from infections in AML is 10% with higher rates seen in patients over the age of 60.[2] To reduce the duration and severity of neutropenia and therefore the risk of infection, granulocyte colony stimulating factors (GCSF) are used to stimulate the production of neutrophils.[3] GCSF has a half life of 3.5 hours, however the addition of a polyethylene glycol protein to GCSF to produce pegfilgrastim, increases its half life to 10 to 14 days.[4]

The evidence to support pegfilgrastim use in acute leukaemia is not well established. Recommendations from the literature and professional bodies vary as pegfilgrastim has shown to reduce the duration of neutropenia by 1 day but not improve all cause mortality, overall survival and occurrence of bacteraemia or invasive fungal infections.[5]

At The Alfred, patients who receive chemotherapy for AML or ALL may receive pegfilgrastim 6mg subcutaneously to aid neutrophil recovery. However, clear guidance on which patients should receive pegfilgrastim is not available. Therefore further research is required to establish if pegfilgrastim is of benefit in our current adult AML and ALL population.

Pegfilgrastim is eliminated from the body by circulating neutrophils. Therefore the duration of action of pegfilgrastim and its efficacy may be reduced if administered before patients reach their neutrophil nadir.

Aim

To evaluate the association between the administration of pegfilgrastim in adults with AML and ALL and the duration of neutropenia, incidence of febrile neutropenia and related negative outcomes such as febrile neutropenia, documented infections, readmission, mucositis and increased length of stay.

To evaluate the association between the duration of neutropenia and the timing of pegfilgrastim administration with respect to neutrophil nadir.

Methods

A retrospective cohort study of adult AML and ALL patients admitted to The Alfred from 1st Jan 2014 to 31st July 2017 was conducted. The analysis included AML patients who underwent consolidation chemotherapy with either IDAC-2, Little ICE or HIDAC protocols; and ALL patients treated with the Hyper CVAD protocol (A cycle and B cycle). Outcomes were assessed per chemotherapy cycle. Data was collated from medical and dispensing records.

Patients undergoing induction chemotherapy, enrolled in clinical trials or treated with filgrastim were excluded. AML and ALL patients were investigated separately for primary and secondary outcomes. Differences in demographic data between groups were adjusted for utilising linear mixture effects modelling.

Results

A total of 48 patients with AML (68 consolidation chemotherapy cycles) and 19 patients with ALL (57 chemotherapy cycles) were included. There was no statistically significant differences in demographic data in the AML or ALL cohorts between the non-pegfilgrastim and pegfilgrastim groups (Table 1); except a higher proportion of poor risk patients in the non-pegfilgrastim AML group (14 vs 1, p=0.04).

Table 1: Demographics

	AML			ALL		
	Non-PegF (n=33)	PegF (n=15)	p value	Non-PegF (n=6)	PegF (n=13)	p value
Age years, median (range)	52 (18-69)	44 (18-67)	0.082	49 (22-66)	47 (21-64)	0.948
Male gender, n (%)	20 (61)	5 (33)	0.120	6 (100)	9 (69)	0.255
BSA m^2, median (range)	1.84 (1.45-2.6)	1.81 (1.38-2.13)	0.272	2.02 (1.93-2.33)	2.00 (1.2-2.22)	0.292

Results

In both AML and ALL the duration of neutropenia was significantly less for those who received pegfilgrastim (Table 2). Secondary outcomes are detailed for AML in Table 3 and for ALL in Table 4.

When pegfilgrastim was used, the duration of neutropenia was shorter when it was administered at the time the neutrophil count was >1x10^9/L (Table 5).

Table 2: Primary outcome - duration of neutropenia (neutrophil count <0.5x10^9/L)

AML	No PegF (days) (n=44)	PegF (days) (n=24)	p value
Duration of neutropenia	15.13 ± 0.77	11.83 ± 1.06	0.018

ALL	No PegF (days) (n=13)	PegF (days) (n=44)	p value
Duration of neutropenia	11.81 ± 0.93	6.46 ± 0.51	<0.001

Table 3: AML secondary outcomes

AML	Non-PegF (n=44)	PegF (n=24)	p value
Readmission *	54%	63%	0.728
Febrile neutropenia	66%	58%	0.603
Documented Infection	36%	21%	0.273
Mucositis	32%	29%	1.000
Length of stay, median (IQR)	25 days (18 -27)	19 days (10-23)	0.011

** Readmission data relate to the 34 (50%) AML patients discharged during the neutropenic period*

Table 4: ALL secondary outcomes

ALL		Non-PegF (n=13)	PegF (n=44)	p value
Readmission*		100%	45%	0.048
Febrile neutropenia		85%	41%	0.010
Documented Infection		61%	23%	0.015
Mucositis		36%	30%	0.722
Length of stay, median (IQR)	**A**	26 days (19 - 28)	14 days (6 – 16)	0.004
	B	14.5 days (9– 19)	13.5 days (9 – 18)	0.448

** Readmission data relate to the 20 (54%) ALL patients discharged during the neutropenic period*

Table 5: Duration of neutropenia for patients receiving pegfilgrastim, with respect to neutrophil count at time of pegfilgrastim administration

AML	Neutrophils >1 (n=11)	Neutrophils <1 (n=13)	p value
Duration of neutropenia, median (IQR)	9 days (7.5- 12)	13 days (10 – 16)	0.026

ALL	Neutrophils >1 (n=35)	Neutrophils <1 (n=9)	p value
Duration of neutropenia, median (IQR)	5 days (4 – 7.5)	8 days (8 – 9)	0.015

Discussion

The limited available literature describes a one day reduction in the duration of neutropenia following pegfilgrastim use in acute leukaemic patients,[5] however our retrospective analysis demonstrated a greater reduction of 3-5 days. This may be due to less toxic chemotherapy regimens currently in use. For example, in AML treatment, cytarabine was dosed at 3g/m^2 until 2011 when dosing at 1.5g/m^2 was found to have similar efficacy with less toxicity.[6]

The ALL cohort obtained the greatest benefit from pegfilgrastim utilisation with regard to secondary outcomes, potentially due to the lower intensity of agents used in the Hyper CVAD protocol.

On occasions pegfilgrastim will be administered once patients are neutropenic to ensure the full effect of the drug is obtained. Our results indicate that the duration of neutropenia was longer when administration was postponed until neutropenia, therefore negating theoretical benefits of delaying administration.

Given the varied recommendations in the literature and professional guidelines regarding the use of pegfilgrastim in acute leukaemia, this study demonstrates that at The Alfred, the duration of neutropenia is reduced and patients with ALL will experience the most benefit from pegfilgrastim administration.

References

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