

## Does dose-escalated filgrastim improve clinical outcomes following autologous stem cell transplantation?

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Conflict of Interest: None

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### Learning Objectives

- Describe the range of G-CSF (filgrastim) doses used in clinical studies and the effect of dose on neutrophil engraftment.

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### Granulocyte-stimulating factor dose-response

- Healthy volunteers  
Incremental increase in neutrophil count with increased G-CSF dose from 75mcg to 600mcg
- Dose dependent response in patients with non-myeloid malignancies at doses between 1-70mcg/kg
- Incremental improved stem cell collection with higher mobilization doses from 5 to 20mcg/kg

• Wang L et al. *Journal of Pharmacokinetics and Pharmacotherapeutics* Vol.28, No.4 Aug 2001  
 • Dührsen U et al. *Blood*. 1988; 72: 2074-81  
 • Engelhardt M et al. *JCO* Vol.17, No. 7 2160 July 1999

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### Pivotal filgrastim randomized trials following autologous transplantation

- 1<sup>st</sup> trial- time to engraftment(days) in mixed diagnosis autografts(n=54)
  - Results: placebo (21d) vs 10mcg/kg (11d) vs 30mcg/kg (14d)
- 2<sup>nd</sup> trial- time to engraftment (days) in NHL autografts (n=44)
  - Results: placebo (21d) vs 10mcg/kg (10d) vs 20mcg/kg (10d)
- Conclusion: Package insert recommends 10mcg/kg/day (reduce to 5mcg/kg/day once ANC>1000)

Stabel RA et al. *J Clin Oncol*. 1994 Sep;12(9):1931-8.  
 Schmitz N et al. *Bone Marrow Transplant*. 1995 Feb;15(2):261-6.

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### Lower-dose filgrastim randomized studies

- Wide variety of clinical studies which differ in:
  - Dose (range: 50mcg/m2 to 7.5mcg/kg)
  - Initiation date post-transplant (range: day 0 to day+10)
  - Conditioning regimen
  - Diagnosis
  - Target neutrophil count end-point (range: 500-1500 cells/ml)

Klump TP et al. *J Clin Oncol*. 1995;13:1323-1327.  
 Cijada E et al. *Bone Marrow Transplantation*. 1999;24:601-607.

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### Continued

- Results are difficult to compare due to heterogeneity in study design, however the results generally show autograft recipients have a modest improvement in time to engraftment (range: 1-6 days)
- The most commonly used dose in low-dose filgrastim studies is 5mcg/kg/day
- ASCO 2006 guidelines recommend 5mcg/kg/day
- To date, filgrastim 5 and 10mcg/kg/day have not been directly compared for patients who undergo autologous stem cell transplantation

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### Delayed engraftment

- Delayed recovery after autologous hematopoietic stem cell transplantation despite infusion of an adequate number of CD34+ cells/kg and clinically stable status:
- Estimated to occur in 5-10% autografts
- Main predictive factor for delayed recovery was the number of nucleated cells in the graft
- Associated with increased morbidity and mortality

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### Potential Cost

- Redbook 2010 (AWP) : \$ 275/300mcg vial and \$438/480mcg vial
- Median # of G-CSF days=8
- G-CSF cost range (median): \$2100-\$3500
- NMH autologous HSCT daily hospital cost: \$150-250K or 10k/day

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## Northwestern Memorial Hospital Initiative

In 2010, practitioners at NMH agreed to change the conventional filgrastim dose (5mcg/kg/d) to 10mcg/kg/day given as a twice daily subcutaneous injection in order to assess the potential clinical benefit of escalated filgrastim dose on:

- Time to engraftment
- Time to hospital discharge
- Febrile Neutropenia
- Number of documented infections
- Day +100 mortality

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## Comparative filgrastim dose escalation study

- Observational Study to compare filgrastim 5mcg/kg to 10mcg/kg
- Inclusion criteria
  - Consecutive autograft patients who were treated with filgrastim 5mcg/kg/d during the year 2008
  - Consecutive autograft patients who were treated with filgrastim 10mcg/kg/d during the year 2010
- Dose initiated day +5 post transplantation
- All patients received a minimum 5mcg/kg/dose
- Dose rounded to nearest vial size
- Target ANC >500 cells end-point

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## Statistics

Statistical analyses were performed by using t-test for difference in group means of continuous variables.

Chi-square or Fisher Exact test were used for difference in frequency counts of categorical variables.

Kaplan-Meier (KM) survival analysis was performed to compare overall survival at 100 days post-transplant between single and twice daily dosed G-CSF treated patients

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Demographics			
TABLE 1. Single versus Twice Daily G-CSF			
Demographics	Single Daily Dose (%)	Twice Daily Dose(%)	p-value
Number	172	182	
Age (range)	56(22-77)	57(24-77)	0.4343
Weight (median/kg)	82.77	85.43	0.2228
Number of patients who received G-CSF 480 mcg/dose (%)	148(86)	148.(91)	0.1877
Male	101(59)	120(66)	0.8711
Diagnosis			
Myeloma	135(78)	136(75)	0.3787
NHL	24(14)	24(13)	0.877
Other	13(8)	22(12)	0.2199
CD34 cells infused(mean-mil/kg)	6.03	6.72	0.0395

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Results			
Results	Single	Twice Daily	P-value
Number of G-CSF treatment days	8(5-21)	8(6-40)	0.8675
Time to engraftment (days)	12	11	0.9126
Length of stay (range)	16(7-45)	16(9-115)	0.4777
Number of patients with microbiologically confirmed infection	26	42	0.0787
Hospital mortality	3(1.7)	4(2.2)	0.99

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Single versus twice daily filgrastim			
Days to Engraftment	Single Dose	Twice Daily Dose	P-Value
<= 10	24	30	0.2986
11	57	62	0.3611
12	60	41	0.0735
13	19	11	0.1860
>= 14	11	15	0.4147

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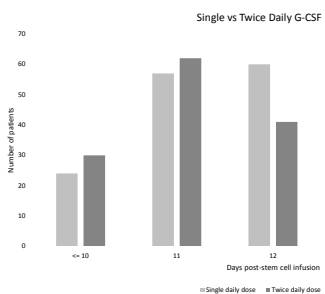
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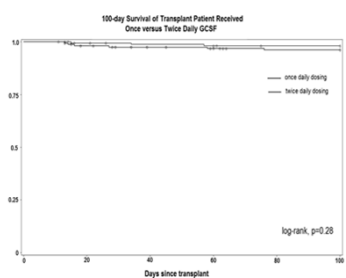
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## Single versus twice daily granulocyte-stimulating factor



## 100 Day Survival



## Conclusion

- Filgrastim dose intensification was not associated with improvement in:
  - Time to engraftment
  - Hospital length of stay
  - Delayed engraftment
- A trend towards increased number of documented infections was observed in the dose-intense arm
- Filgrastim cost was significantly higher in the dose-intense arm

### Audience Response Question

- Dose escalated-filgrastim has been shown to improve which of the following clinical outcomes?
- A. Time to engraftment
- B. Reduction in documented infections
- C. Cost
- D. A and C
- E. None of the above

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