Efficacy of late Hematopoietic Stem Cell Mobilization 35-40 hours after administration of Plerixafor

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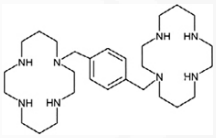
Plerixafor



Cyclam Rings connected by a Methylene linker

Learning Objective

- Compare the efficacy of Plerixafor when administered during and beyond the recommended 10 to 14 hour (vs 35 to 40 hrs) window before stem cell collection

Plerixafor in Hematopoietic Stem Cell Mobilization

- CXCR4/CXCL12 interaction important in retention of HSC in bone marrow
- Plerixafor inhibits CXCR4 receptor, blocking binding with CXCL 12
- Initially investigated as an anti-HIV drug
- Can overcome known risk factors for poor stem cell mobilization
- Reduces mobilization failure rate from 30% to <10%

Fricker SP et al Biochem Pharmacol 2006

Plerixafor: Pharmacology

- Pivotal study in C3H/HeJ mice: peak CFU (colony forming units) 1hr after s/c injection, dose dependant and returned to baseline in 24 hours

Humans

- Peak plasma concentration 30mins after s/c administration
- Elimination half life of 4.6 hours
- Peak CD34+ cells 10-14 hours after dose
- Synergistic effect with G-CSF

Broxmeyer HE et al, J Exp Med 2005

Harvey RD et al Biol Blood Marrow Transplant 2013

Temporal restrictions in Plerixafor Administration

- Labeling requires administration approximately 11 hours before apheresis-> administration 10pm followed by collection next morning
- Limited data in humans on effect on hematopoietic stem cell collection beyond the 14 hour period
- Successful mobilization with administration 17 hrs prior to apheresis-> administration 4pm followed by collection next morning

Harvey RD et al Biol Blood Marrow Transplant 2013

Late HSC Mobilization Post Plerixafor

- Retrospective analysis
- Total Number: 7 (3M/4F)
- Age: 39-72 years; Median 69
- Diagnosis:
  - Multiple Myeloma 5
  - Non-Hodgkin Lymphoma 2
- Prior Chemotherapy
  - 6/7 ≥ 3 prior chemotherapy regimens
  - 1/7 Hyper-CVAD 8 cycles

Mobilization Regimens

- G-CSF + Plerixafor: 1
- Chemotherapy Mobilization 6
  - DPACE/DCEP+GCSF+Plerixafor 3
  - Hyper-CVAD+GCSF+Plerixafor 1
  - Cylophosphamide+GCSF+Plerixafor 1
  - RICE+GCSF+Plerixafor 1

Indication for Plerixafor Administration

- Peripheral CD34 + > 10/µl, with failed mobilization (CD34+ 12.1/µl) 1
- Peripheral CD 34+ < 10/µl 6
- (0.17-5.29/µl, Median 0.99/µl)
- Drug was administered only in patients failing mobilization

Dosage and Timing

- 0.24mg/kg subcutaneously
- Timing: 11-17 hrs prior to apheresis
- First day of Plerixafor administration (Day 1:1st day of chemotherapy/G-CSF)
  - Combination Chemotherapy 15-19
  - Cyclophosphamide 14
  - G-CSF alone 6
- Plerixafor administered till minimum target CD34+cells/ kg body weight achieved ($2x10^6$ / $4x10^6$ CD34+ cells/ kg)
- Additional collection following day with G-CSF alone: 35-40 hours after last dose of Plerixafor
- Total Number of Doses 1-4 (Median 3)

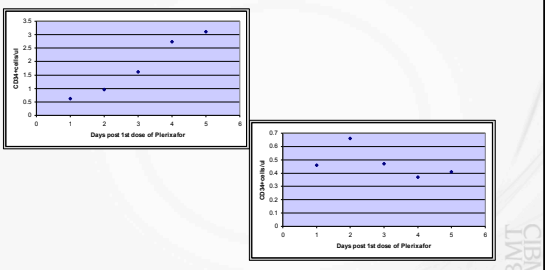
CD34+ cells(/µl) collection 11-16 hours & 35-40 hours post Plerixafor

DIAGNOSIS	MOBILIZATION REGIMEN	11-16 HOURS	35-40 HOURS
Myeloma	DPACE	3.12	3.13
Myeloma	DPACE	2.19	2.37
Myeloma	DCEP	0.72	0.78
NHL	CYCLOPHOS	0.37	0.41
NHL	RICE	2.74	3.11
Myeloma	HYPERCVAD	4.21	5.25
Myeloma	No Chemo	0.73	1.4

CD34+ collection: 11-16 hrs vs. 35-40 hrs post G-CSF + Plerixafor

- Average collection 11-16 hours : 0.49-4.21 (Total 1-4 days, Median 3) Mean 1.21
- Collection 11-16 hours post last dose: 0.37-4.21 Mean 2.01
- Collection 35-40 hours post last dose: 0.41-5.25 Mean 2.21
- Collection in patient with G+P alone:
  - 11 hours 0.73
  - 35 hours 1.40

Daily HSC Collection Trend



Possible Explanations for Late HSC Mobilization post Plerixafor

- Unusual patient population
- Late count recovery with continued effect of G-CSF
- Kinetics of Plerixafor effect on CD34+ cells in humans remains to be properly understood

Conclusions

- Collection 35-40 hours post last dose of Plerixafor was superior/comparable to the traditional 11-14 hour window
- Need for additional studies to determine the effects of Plerixafor on CD34+ cells beyond the 11-14 hour period
- Alternate Plerixafor mobilization protocols possible with significant cost implications

Quiz Time

Plerixafor in stem cell mobilization

Which of the following statements is correct with regards to this study?

A. Patients were at average risk for mobilization failure and had superior PBSC collection 35 hours post Plerixafor

B. Patients were at high risk for mobilization failure and had superior collection in the traditional 11-16 hours post Plerixafor

C. Patients were at high risk for mobilization failure and had superior/comparable collection 35-40 hours post Plerixafor

D. Attempting to collect PBSC beyond the day after last dose of Plerixafor is futile and is waste of resources

THE END