PREDICTORS OF ENGRAFTMENT IN AUTOLOGOUS STEM CELL TRANSPLANTATION.

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Background

- Hematopoietic stem cell transplantation (HSCT) plays an important role in restoring hematopoiesis after intensive myeloablative therapy in patients with hematologic malignancies.
- **Neutrophil recovery(ANC engraftment)** : first day of 3 consecutive days when neutrophil count above 500/ul
- **Platelet recovery(engraftment)** :first day of 3 consecutive days when Platelet count is >20,000/μl, independent of platelet transfusion

Aim of the study

- To assess factors predicting engraftment among patients undergoing autologous peripheral blood stem cell transplantation for hematological malignancies.

Materials and methods

- Retrospective analysis of patients who underwent autologous stem cell transplant at a tertiary care centre in Kerala ,South India from January 2013 to July 2016 .
- Stem cell Mobilization was done using either GCSF alone GCSF and cyclophosphamide or GCSF and plerixafor.
- All the apheresis performed using Cobe spectra apheresis system and spectra optia ,Terumo BCT as per protocol.

Materials and methods

- CD 34^{+} cell pre-counts using flow-cytometry following the recommendations of the International Society of Hematology and Graft Engineering (ISHAGE).
  - perepheral blood on the day of apheresis procedure
  - apheresis product
- Hematologic recovery was defined from the day of stem cell infusion (day 0).

Statistical analysis

- Variables were compared using Kruskal wallis test and Mann whitney test was used to obtain statistical difference of mean differences.
- Survival analysis was done using Kaplan-meier analysis
- Survival comparison using Log rank test.
- All analyisis done using IBM SPSS version 20.0

Results & discussion

Characteristic	
Number of patients	38
Gender (male/female)	23(61%)/15(39%)
Age	52 yrs (3-64)
Disease	
Multiple myeloma	27(71%)
Lymphoma	7(18%)
Leukemia&others	4(11%)
Myeoablative conditioning regimen	
Melphalan 200 mg/m^2 BSA	22(57.9%)
Melphalan 100 mg/m^2 BSA	4(10.5%)
Busulphan +melphalan	1(2.6%)
Busulphan+cyclophospamide	3(7.9%)
BEAM	8(21%)
Median infused CD 34 stem cells/kg body weight ($x10^{6}$)	5.33(2.18-11)
Median infused Mononuclear cells /Kg($x10^{8}$)	7.15(1.93-12.93)
Median number of procedures per patient	2(1-4)

Stem cell Mobilisation

- 20 • GCSF alone
- 2 • GCSF+Cyclophosphamide
- 16 • GCSF+Plerixafor

Mobilisation Regimen	Pre-apheresis cd34		p Value
	Mean	SD	
GCSF Only	51.69	37.27	0.360
GCSF+ Plerixafor	57.57	34.24	

- 47.4 % of patients were poor mobilisers who required either Plerixafor or Cyclophosphamide in addition to GCSF to achieve adequate mobilisation

- Peripheral-blood pre-apheresis wbc and cd34 count correlated significantly with number of harvested CD34 cells per kg recipient body . yield ($r=0.379$ $p=0.019$) and ($r=0.601$; $p<0.001$)

Stem cell mobilisation

- Plerixafor group attained adequate number of CD 34 yield in lesser number of apheresis
  - median 4.8 fold increase in pre apheresis CD 34 count
  - 1.7 fold increase in Gcsf alone.
- (Randomised double blind placebo controlled study). *Di persio etal,blood,2009.*

- In our study ,as only poor mobilisers were given plerixafor, the mean Pre apheresis CD34 count in that group is hence similar to GCSF alone group.

Variables in relation to neutrophil engraftment

97.3 % of patients attained successful ANC and platelet engraftment.

Variables		N	Mean	SD	p Value
Age	≤ 50	17	12.12	4.73	0.005
	>50	20	9.35	0.67	
Diagnosis	Myeloma	27	9.33	0.62	<0.001
	Lymphoma	7	13.43	3.87	
	Others	4	15.67	8.96	
Conditioning regimen	Melphalan	26	9.35	0.63	<0.001
	BuCy & BEAM	12	13.64	5.33	
Cryopreservation	0	24	9.33	0.64	<0.001
	1	13	13.33	5.19	
CD34 /kg($x10^{6}$)	≤ 5	17	9.94	0.93	.473
	> 5	21	11.14	4.53	

Variables in relation to platelet engraftment

Variables	Age	N	Mean	SD	p Value
Age	≤ 50	18	16.06	8.35	0.060
	>50	20	11.00	4.05	
Diagnosis	Myeloma	27	10.70	3.66	.002
	Lymphoma	7	20.86	5.70	
	Others	4	19.33	14.64	
Cryopreservation	0	24	10.24	2.38	.002
	1	13	19.75	8.52	
Conditioning regimen	Melphalan	26	10.77	3.71	.003
	BuCy & BEAM	12	19.36	8.64	
CD34 /kg($x10^{6}$)	≤ 5	17	13.88	5.21	0.146
	> 5	21	12.90	7.89	

Engraftment in relation to CD34 cell yield

- The result imply that CD 34 cell dose has no clear influence on the engraftment kinetics in this study group

Author	Journal	Summary of the result
Alshemmari etal.	Saudi med J 2007	No significant influence of CD 34 dose on ANC engraftment
Spencer etal	Proc AM Soc clin Onco 1992	No correlation between CD34 dose and engraftment
Mortimer etal	Proc AM Soc clin Onco 1993	No correlation between CD34 dose and engraftment

- Many studies have demonstrated significant correlation of engraftment with CD 34 dose
- The optimal CD 34 Dose for successful hematopoetic autologous transplant suggested by authors :

Author	Subjects (N)	Diagnosis	ANC/PLC Engraftment		CD34 + Cells /kg
Haas etal,Blood 1994	46	HL/NHL	14 d	ANC	$\geq 2.5 \times 10^6$
Watts M J etal,1997	81	HL/NHL	28 d	PLC	$\geq 3.5 \times 10^6$

- Heterogenous patient population
- Different conditioning regimens
- Failure of higher cd34 dose to further accelerate ANC recovery may be due to standard practice of giving growth factors after transplantation in higher and lower groups

Engraftment in relation to Age

Age	Design	Observation	Author	discussion
50-59 yr	Retrospective study	Better engraftment	Goncalves etal,2009. Brazil	Patients in older age group got favourable conditioning regimen,M-200 which are asso with faster engraftment
>50 yrs	Retrospective study	Better engraftment	Our study	

- Delayed engraftment with cryopreservation due to
  - Probable cell loss during the process
  - Disease type
  - Conditioning in this group (Especially leukemia)

Engraftment in relation to Disease type & conditioning regimen

- Our study showed engraftment is significantly better with multiple myeloma compared to Lymphoma and leukemia
- Patients with multiple myeloma were given Melphalan 200 which showed rapid engraftment than beam/busulfan containing protocol *Goncalves etal ,2009*
- Leukemia group had delayed recovery and said residual leukemia could be a cause for this *Carral etal 2002*

ENGRAFTMENT DAYS IN RELATION TO PLATELET TRANSFUSION

Variable	Platelet engraftment	
	Correlation Coefficient	p Value
Platelet transfusion before platelet engraftment	0.858	<0.001

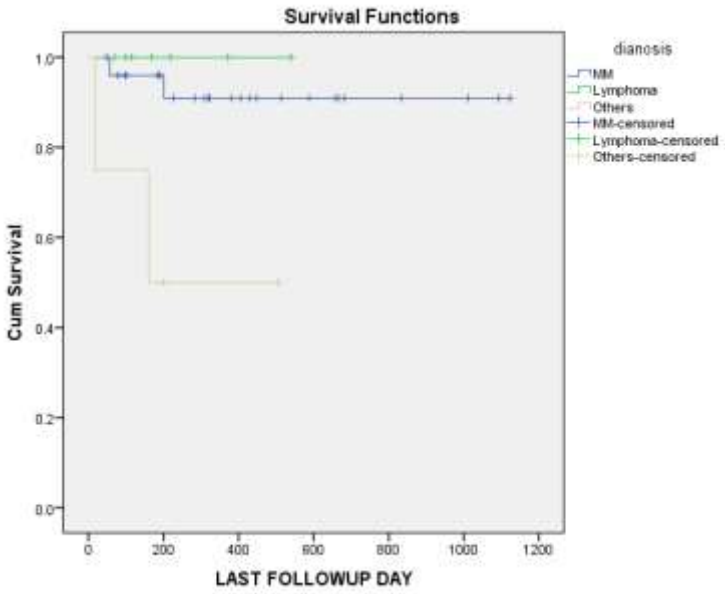
Author	Summary of the results	
Salazar etal ,1996	More platelet transfusion for patients receiving $<5x10^6$ than those getting $>5 \times 10^6$	P<0.05
Kiss etal ,1997	More platelet transfusion for patients receiving $<5x10^6$ than those getting $>5x10^6$	p=.007

Overall survival

- One (2.6 %) patient died at 18 days after transplantation before engraftment was fully assessable
- 89% (34 out of 38)survived
- No significant difference in survival on the basis of cd34 yield
  - CD 34 yield < 5
    - Mean survival 878±86.75 days
  - CD 34 yield > 5
    - Mean survival 1017±70.03 days
- No significant difference in survival on the basis of age
- 50 yrs agegroup,
  - 6month& one year survival probability is 81.4% & 81.4%
- >50 yrs age gp,
  - 6month & one year survival probability is 100% &92.9 %
  - p value :0.35

BASED ON DISEASE TYPE

- Survival
  - Multiple myeloma : 91.9%
  - Lymphoma : 100%
  - Leukemia : 50%
- Significant difference in survival of multiple myeloma & lymhoma (p=0.021)



No significant difference (p=0.309)in survival based on conditioning regimen

Overall survival

- OS was better in myeloma compared to leukemia

- Goncalves etal,2009 reported a similar result and it could be because of the toxicity associated with busulfan,cyclophospahamide in patients with leukemia.

SUMMARY

- CD 34 dose if above >2 x 10^6 is adequate for hematopoetic recovery
- Eliminates the need for additional apheresis sessions
  - Reduce the cost
  - Reduce tumour cell contamination
- Variables like Conditioning regimen ,disease type ,age influenced the engraftment
- Need of supportive treatment like transfusions will depend upon engraftment kinetics

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Thank You!