Transplant outcomes and data analysis

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What are outcomes?

- Assessments which gauge the effect, or results, of treatment for a particular disease or condition
- Outcomes can include measures of mortality, morbidity, cost, quality of life, patient satisfaction, and many others

Outcomes after a SCT

?????

Outcomes after a SCT

- Neutrophil engraftment
- Platelet engraftment
- Acute Graft vs Host Disease
- Graft failure
- Chronic Graft vs Host Disease
- Disease Relapse
- Mortality

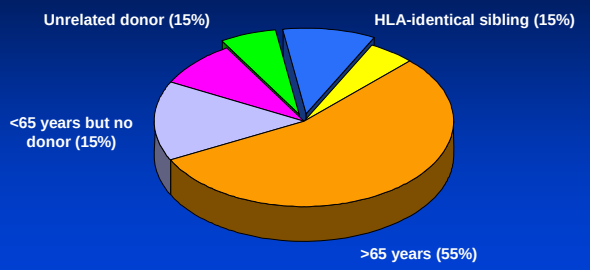
Other SCT outcomes

- CMV activation / re-activation
- Hospitalisation days
- Karnofsky score
- Lung performance
- Fertility
- Long-term effects

Patients who receive a SCT

- Can we say anything about causes of their disease?
- Is this population representative?

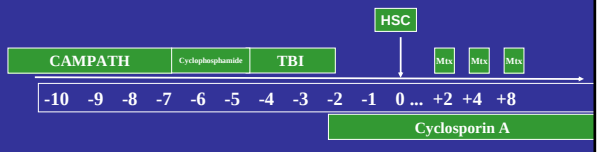
Eligibility of allo-SCT for patients with CML



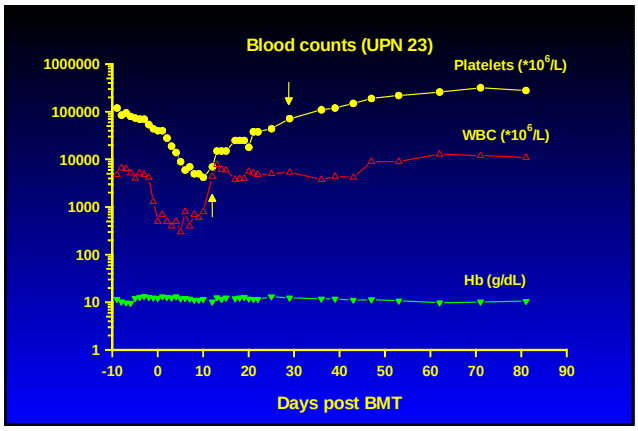
SCT – course of events

- Days 7 – 40 - Engraftment
- > Day 28 – Graft failure
- > Day 7 – Acute graft versus host disease
- > Day 0 – Disease progression, relapse
- > Day 0 – Death from any causes
- > Day 100 – Chronic graft versus host disease

UD-SCT: conditioning



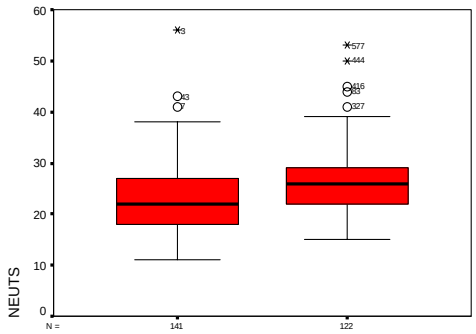
TBI: 14.4 Gy in 6 fractions (240 cGy bd x 6) (days -4,-3,-2)
Cyclophosphamide: 60 mg/kg od x 2 (days -6 and -5)
Campath: 10 mg od x 5 (days -10 to -6)
Cyclosporin A: 2.5 mg/kg od (day -3 onwards)
Methotrexate: 8 mg/m^2 od (days +2, +4, +8)

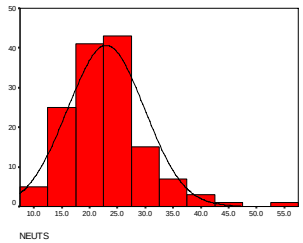


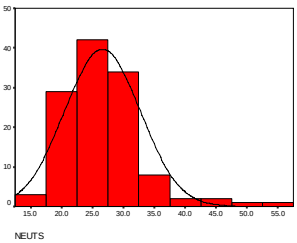
Neutrophil engraftment following allogeneic SCT for CML

		Cases					
		Valid		Missing		Total	
	TBIDOSE	N	Percent	N	Percent	N	Percent
NEUTS	12	141	88.1%	19	11.9%	160	100.0%
	14.4	122	95.3%	6	4.7%	128	100.0%

TBIDOSE				Statistic	Std. Error
NEUTS	12	Mean		**22.9787**	.5816
		95% Confidence Interval for Mean	Lower Bound	21.8289	
			Upper Bound	24.1286	
		5% Trimmed Mean		22.5816	
		Median		**22.0000**	
		Variance		47.692	
		Std. Deviation		6.9060	
		Minimum		11.00	
		Maximum		56.00	
		Range		45.00	
		Interquartile Range		9.0000	
		Skewness		1.162	.204
		Kurtosis		3.184	.406
	14.4	Mean		**26.6148**	.5544
		95% Confidence Interval for Mean	Lower Bound	25.5172	
			Upper Bound	27.7123	
		5% Trimmed Mean		26.1184	
		Median		**26.0000**	
		Variance		37.495	
		Std. Deviation		6.1233	
		Minimum		15.00	
		Maximum		53.00	
		Range		38.00	
		Interquartile Range		7.2500	
		Skewness		1.453	.219
		Kurtosis		4.157	.435







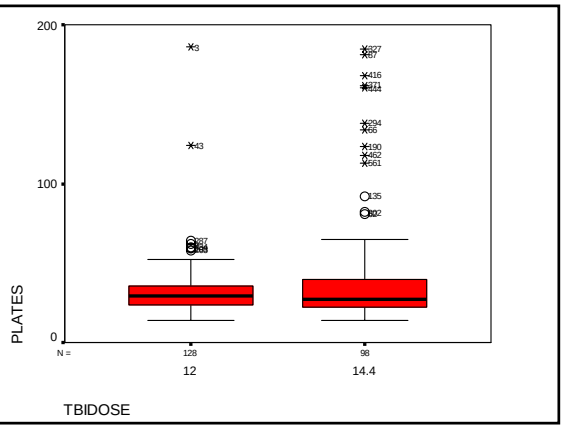
Platelet engraftment following allogeneic SCT for CML

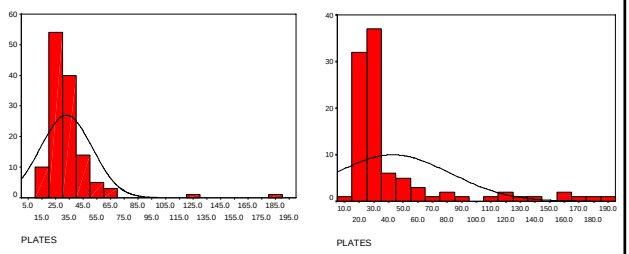
Platelet engraftment following allogeneic SCT for CML

		Cases					
		Valid		Missing		Total	
	TBIDOSE	N	Percent	N	Percent	N	Percent
PLATES	12	128	80.0%	32	20.0%	160	100.0%
	14.4	98	76.6%	30	23.4%	128	100.0%

Descriptives

TBIDOSE				Statistic	Std. Error
PLATES	12	Mean		**32.7891**	1.6694
		95% Confidence Interval for Mean	Lower Bound	29.4857	
			Upper Bound	36.0924	
		5% Trimmed Mean		30.5556	
		Median		**29.5000**	
		Variance		356.703	
		Std. Deviation		18.8866	
		Minimum		14.00	
		Maximum		186.00	
		Range		172.00	
		Interquartile Range		11.7500	
		Skewness		5.244	.214
		Kurtosis		37.479	.425
	14.4	Mean		**42.8776**	3.9481
		95% Confidence Interval for Mean	Lower Bound	35.0417	
			Upper Bound	50.7134	
		5% Trimmed Mean		37.1973	
		Median		**27.0000**	
		Variance		1527.572	
		Std. Deviation		39.0842	
		Minimum		14.00	
		Maximum		185.00	
		Range		171.00	
		Interquartile Range		18.0000	
		Skewness		2.368	.244
		Kurtosis		4.780	.483





Group Statistics

	TBIDOSE	N	Mean	Std. Deviation	Std. Error Mean
NEUTS	12	141	22.9787	6.9060	.5816
	14.4	122	26.6148	6.1233	.5544
PLATES	12	128	32.7891	18.8866	1.6694
	14.4	98	42.8776	39.0842	3.9481

Independent Samples Test

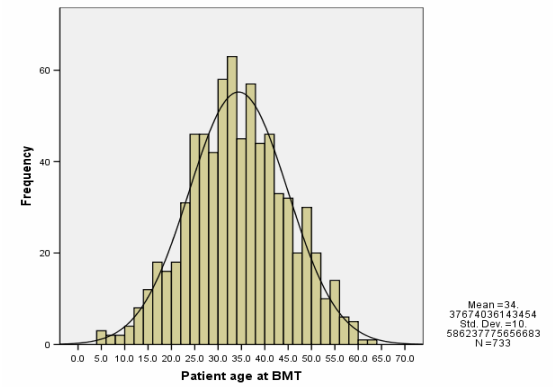
		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
NEUTS	Equal variances assumed	2.291	.131	-4.486	261	.000	-3.6360	.8105	-5.2320	-2.0401
	Equal variances not assumed			-4.525	260.837	.000	-3.6360	.8035	-5.2182	-2.0539
PLATES	Equal variances assumed	28.139	.000	-2.557	224	.011	-10.0885	3.9448	-17.8622	-2.3148
	Equal variances not assumed			-2.354	131.572	.020	-10.0885	4.2865	-18.5679	-1.6091

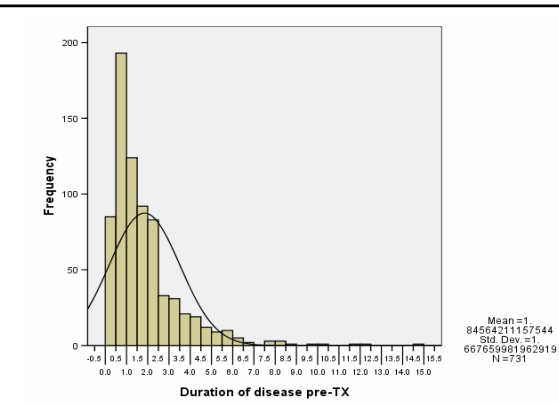
Comparison of platelet and neutrophil engraftment at two different TBI doses

	PLATES	NEUTS
Mann-Whitney U	6172.500	5543.500
Wilcoxon W	11023.500	15554.500
Z	-.204	-4.977
P-value (2-tailed)	**0.83**	**0.0006**

Comparison of neutrophil and platelet engraftment at two different TBI doses - summary

- Neutrophil engraftment took approx 2 days longer at 14.4Gy compared with 12Gy and was highly statistically significant (p=0.0001)
- Platelet engraftment took approx 2 days less at 14.4Gy compared with 12Gy but this was not statistically signficant (p=0.83)





Acute Graft versus Host Disease

- Example of an outcome which is graded

agvhdg

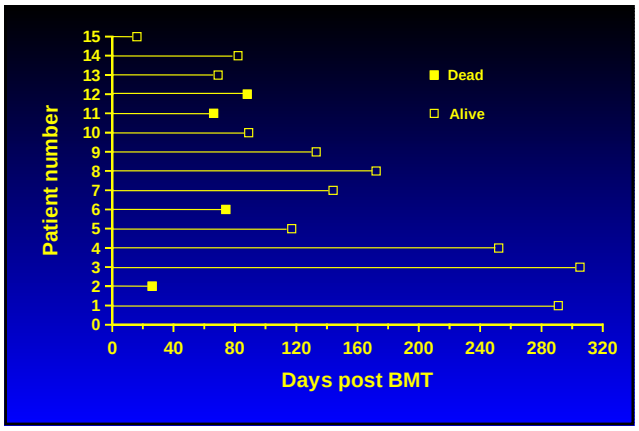
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Nil	181	24.7	25.7	25.7
	1	150	20.5	21.3	47.1
	2	222	30.3	31.6	78.7
	3	85	11.6	12.1	90.8
	4	65	8.9	9.2	100.0
	Total	703	95.9	100.0	
Missing	System	30	4.1		
Total		733	100.0		

Mortality

- On treatment A – 20 out of 30 patients are alive
- On treatment B – 12 out of 30 patients are alive
- If we compare the treatments using a Chi-squared test – then Treatment A is better (p=0.04)
- Is this the correct approach?

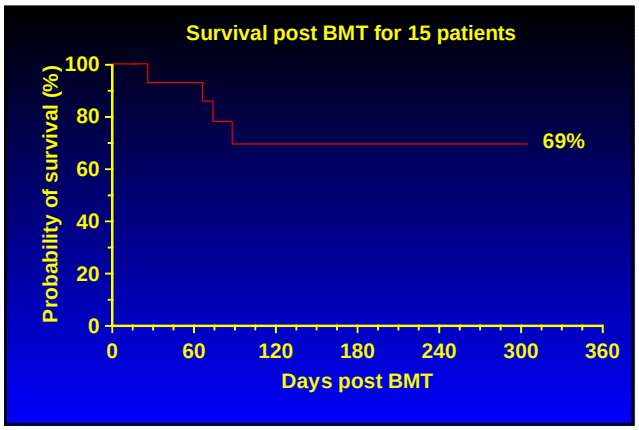
Survival Analysis

- Events may occur at variable time points post transplant – so in statistical terms – each has 2 components 1.) whether the event occurs, and if it does 2.) time to the event
- However, the event of interest may not occur – and so the data needs to be 'censored'
- The inclusion of data that is censored requires special statistical treatment



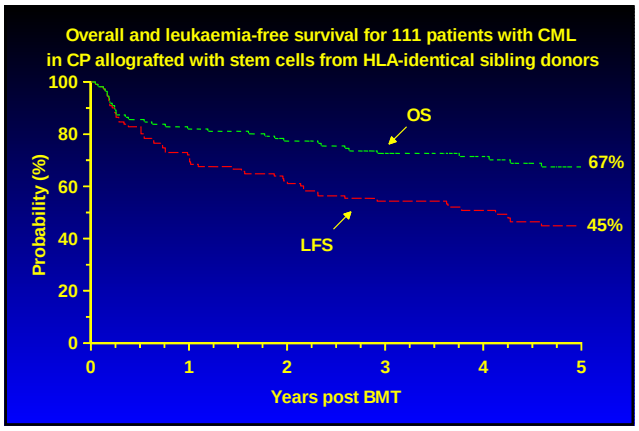
Life table for fifteen patients who received an allogeneic SCT

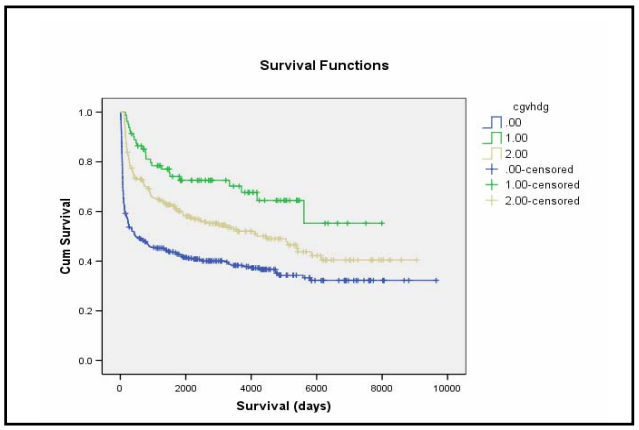
Time (days)	Status	Number at risk	Probability of survival	Standard error
16*	0	15	1.00	
26	1	14	0.93	0.069
66	1	13	0.86	0.094
69*	0	12		
74	1	11	0.78	0.113
82*	0	10		
88	1	9	0.69	0.129
89*	0	8		
117*	0	7		
133*	0	6		
144*	0	5		
172*	0	4		
252*	0	3		
291*	0	2		
305*	0	1		

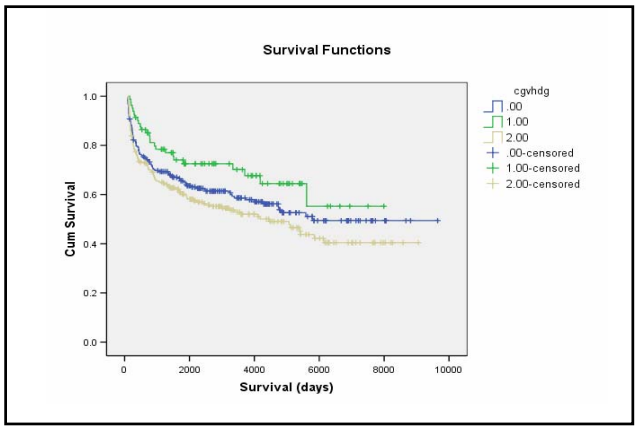


Outcomes suitable for Kaplan-Meier analyses

- Survival - event of interest is death, patients alive are censored
- Disease-free survival - events of interest are either death or disease relapse, patients alive and in remission are censored
- *Primary graft failure*
- *Acute graft versus host disease*

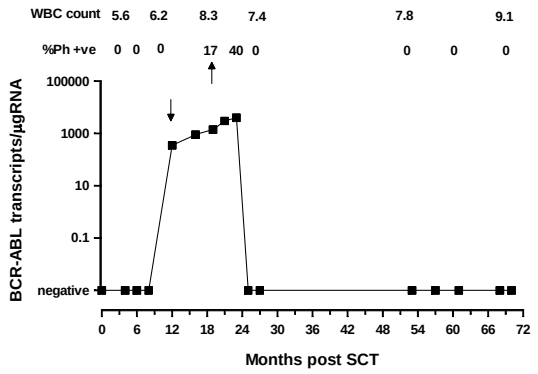

Overall and leukaemia-free survival for 111 patients with CML
in CP allografted with stem cells from HLA-identical sibling donors
Probability (%)
100
80
60
40
20
0
OS
67%
LFS
45%
0
1
2
3
4
5
Years post BMT

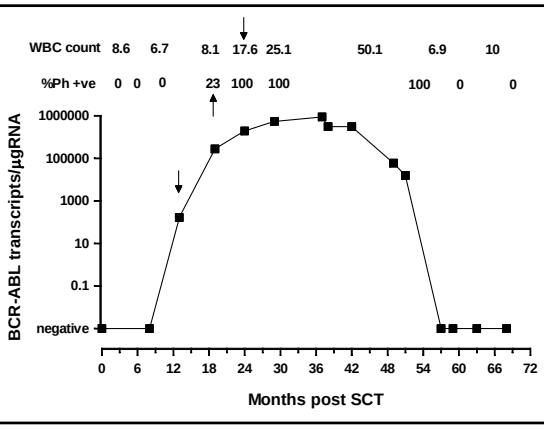

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2000
4000
6000
8000
10000
Survival (days)
cgvhdg
.00
1.00
2.00
.00-censored
1.00-censored
2.00-censored

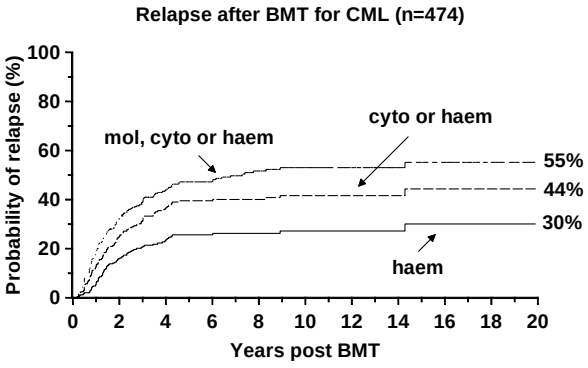

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2000
4000
6000
8000
10000
Survival (days)
cgvhdg
.00
1.00
2.00
.00-censored
1.00-censored
2.00-censored

Relapse in CML

- PCR (Polymerase chain reaction) can be utilised to amplify small quantities of a particular gene to a point where it can be easily detected
- In CML the BCR/ABL gene is amplified, enabling the presence of one CML cell in 100 million to be detected – allowing the possibility of detecting molecular relapses
- If molecular testing is not available, cytogenetic analysis provides the next level of disease detection







Cumulative incidence procedure

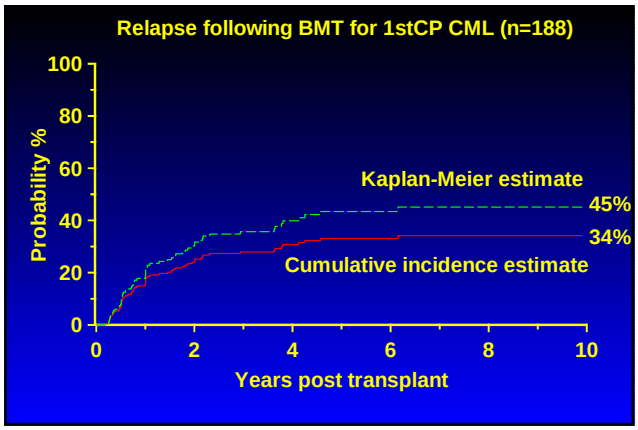
- For some outcomes (AGVHD, TRM, relapse, GF and infections) there is an additional complication to the calculation of the probability
- If the patient dies before the event of interest can occur – this constitutes a 'competing risk'
- The cumulative incidence procedure needs to be applied

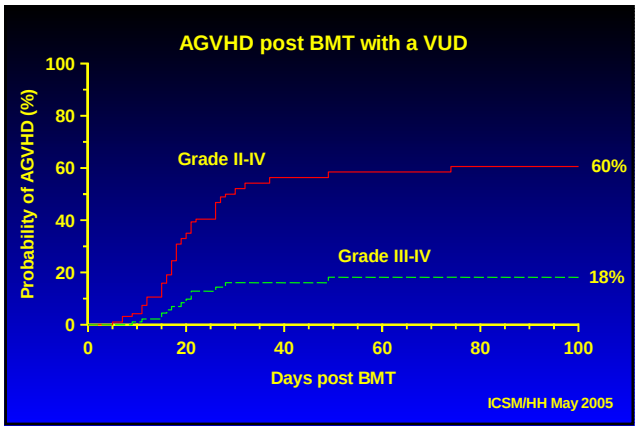
Outcomes suitable for cumulative incidence analyses (1)

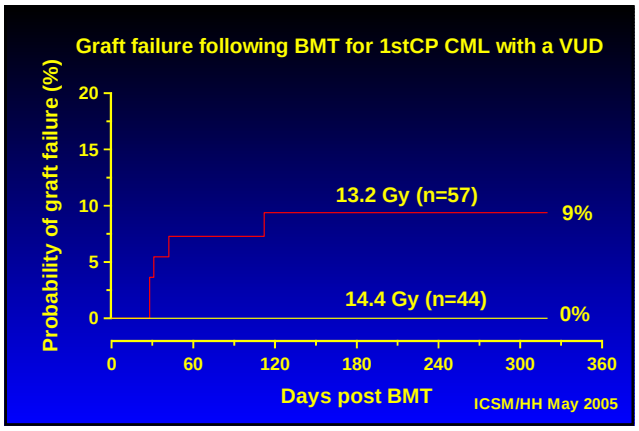
- Relapse - the event of interest is disease relapse, patients alive without disease are censored, whilst death in remission is the competing risk
- Graft versus host disease - the event of interest is the grade of GVHD, patients alive without disease are censored, the competing risk is death without development of GVHD
- Transplant related mortality - the event of interest is death due to the procedure, patients who are alive are censored, deaths due to disease are a competing risk

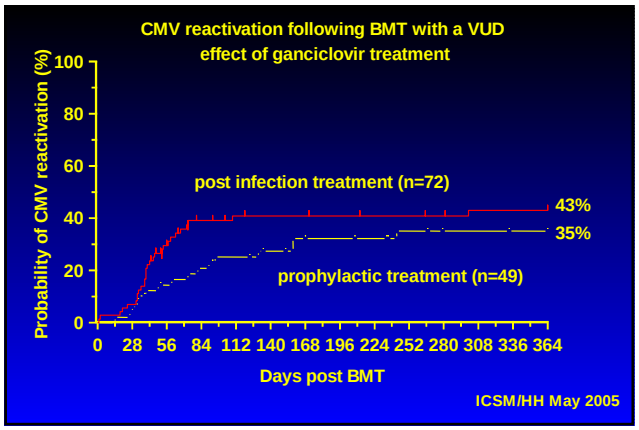
Outcomes suitable for cumulative incidence analyses (2)

- Graft failure - the event of interest is graft failure (non-engraftment), patients who have engrafted and who are alive are censored, the competing risk is death without engraftment
- Infections – the event of interest is the infection, patients who are alive without infection are censored, the competing risk is death before infection taking place



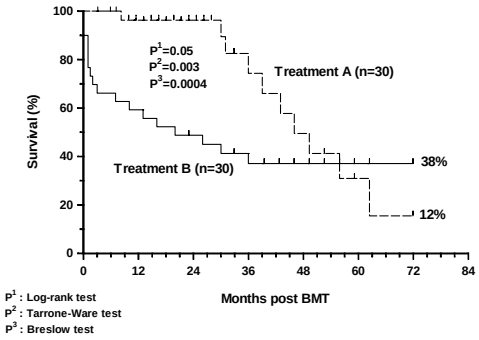


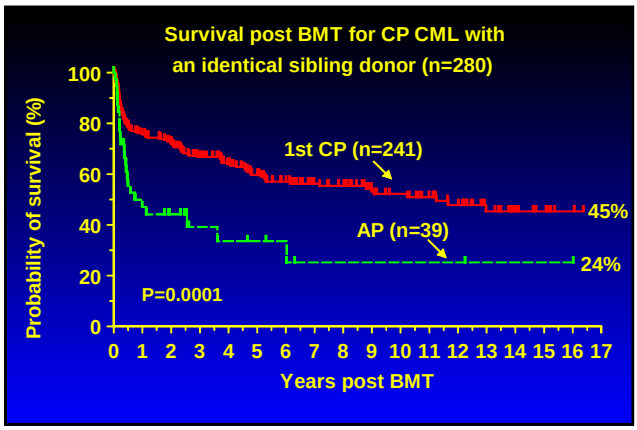




Comparing survival curves

- Survival curves provide a visual assessment for a particular treatment or disease course
- In order to establish a survival advantage, it is necessary to perform a statistical test
- Not appropriate to compare survivors using a chi-squared test
- For example, Treatment A 20/30 vs Treatment B 12/30 (Chi-squared p=0.04, Treatment A is better)
- The time to the event must be taken into account
- Log-rank test compares two life tables



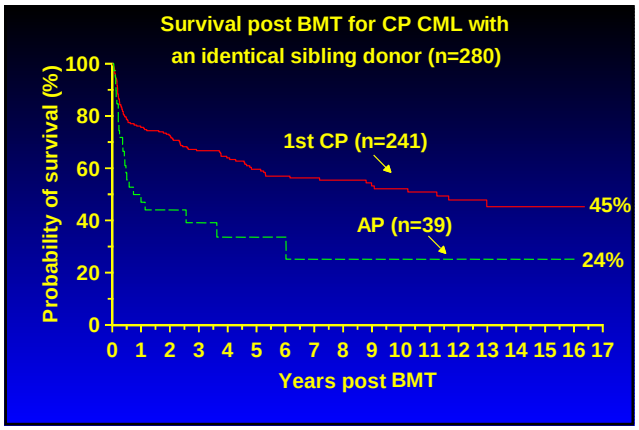


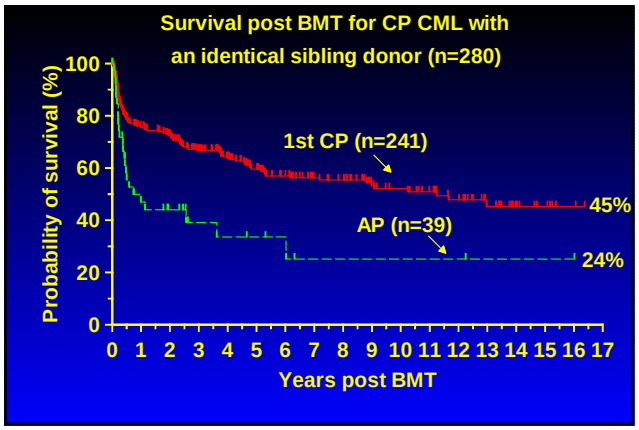
Proportional Hazards Regression Analysis

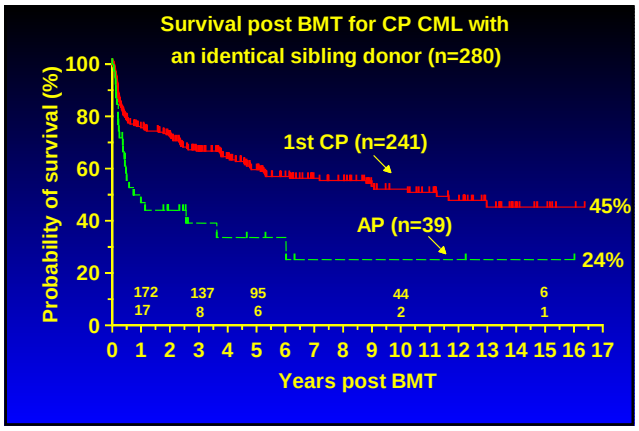
- Allows any number of prognostic variables to be entered into a model at the same time to describe a single outcome
- A selection procedure, based on statistical significance, is usually utilised to find the 'best' model

Multivariate analysis of survival following a mini-allograft for CML

Variable	N	Relative Risk	CI	P
Disease status at transplant				
CP1	115	1.00		
CP2	26	1.20	0.6-2.5	p=0.70
AP	30	3.40	2.0-5.8	p<0.001
BC	12	6.20	3.1-12	p<0.001
Fludarabine +TBI				
No	170	1.0		
Yes	13	2.9	1.3-6.5	P=0.008

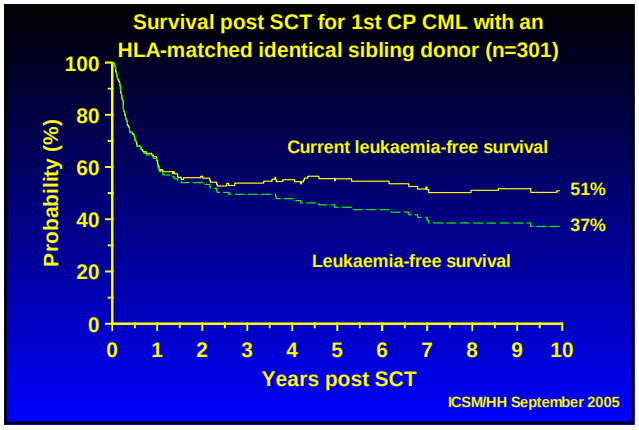






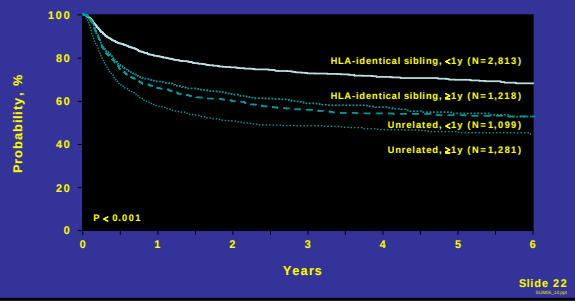
Current leukaemia-free survival

- The ability of salvage therapies such as DLI to restore patients who have relapsed, to complete remission, means that the normal way of reporting LFS has to be modified
- We have recently established current leukaemia free survival (CLFS) as an improved measure of transplant failure



Publications and education

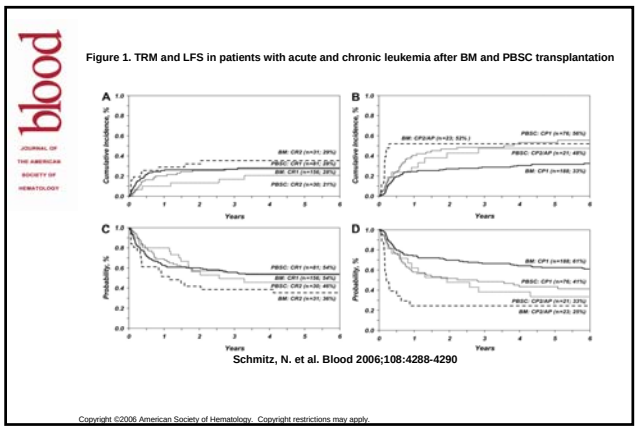
Probability of Survival after Transplants for CML in Chronic Phase, 1998-2004
- by Donor Type and Disease Duration



Long-term outcome of patients given transplants of mobilized blood or bone marrow: A report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation.

Schmitz N, Eapen M, Horowitz MM, Zhang MJ, Klein JP, Rizzo JD, Loberiza FR, Gratwohl A, Champlin RE; International Bone Marrow Transplant Registry; European Group for Blood and Marrow Transplantation.

Blood. 2006 Dec 15;108(13):4288-90



Summary

- The collection of data from transplant programmes is the reason why we are here!
- It is an incredibly important cog in the machinery that is medical progress
- Assessment of outcomes identify prognostic factors, shape new strategies for treatment, and gives patients with a variety of life threatening diseases a better chance of having a normal life