Disclosures

- Investigator-initiated study funded by Astellas

Background

- Widespread use of preemptive therapy strategies has decreased CMV end-organ disease to 5-8% after HCT.
- Implications for development of CMV vaccines and therapeutics.

Background

- Widespread use of preemptive therapy strategies has decreased CMV end-organ disease to 5-8% after HCT.
- Implications for development of CMV vaccines and therapeutics.
- Could the *indirect effects* of CMV infection be useful components of a composite clinical endpoint for CMV prevention trials when, in the era of preemptive therapy, CMV end organ disease is a relatively rare event?

Background

- Acute GVHD
  - Cantoni et al. *BBMT,* 2010.
- Chronic GVHD
  - Kanda et al. *Bone Marrow Transplant.,* 2014.
  - Anderson et al. *Biol Blood Marrow Transplant.,* 2003.
- Infectious complications
  - Nichols et al. *J Infect Dis.* 2002
  - Lengerke et al. *Bone Marrow Transplant*. 2006
  - Green et al. *Biol Blood Marrow Transplant., 2012*

Objectives

Estimate the association between CMV reactivation within the first 100 days after allogeneic HCT and subsequent development of:

- grades II – IV acute GVHD
- chronic GVHD requiring systemic immunosuppressive treatment (NIH consensus)
- bacteremia
- invasive fungal infections.

Study Design

- Retrospective cohort analysis
- Patients with first allogeneic HCT (BM or PBSC)
- 1995-2013 preemptive therapy guided by pp65 antigenemia (through 2006) then PCR (from 2007)
- Research database includes demographic, transplant, clinical, and microbiologic data
- Multivariable Cox proportional hazards models were used to estimate the association between CMV and each of the endpoints

Definitions

- CMV monitored weekly until day 100
- Patients undergo regular evaluation for acute and chronic GVHD
- Acute GVHD is recorded as date of onset and maximal grade achieved (retrospectively determined)
- Fungal infections either “proven” or “probable” by EORTC/MSG consensus
- Bacteremia classified as gram positive, gram negative, other

Cohort characteristics (n= 4394)

		n (%)
Transplant year	1995-2006	2972 (68%)
	2007-2013	1422 (32%)
Age in years	0-18	534 (12)
	19-40	1264 (29)
	41+	2596 (59)
CMV Risk	D-/R+	1210 (28)
	D+/R+	1203 (27)
	D+/R-	542 (12)
	D-/R-	1439 (33)
Myeloablative Conditioning		3245 (74)
Cell source- PBSC		2657 (60)

Cohort characteristics (n= 4394)

	n (%)
HLA	
Matched, related	1779 (40)
Mismatched, related	200 (5)
Matched, unrelated	1937 (44)
Mismatched, unrelated	340 (8)
Haploidentical	128 (3)
Unknown	10 (0)

CMV viremia and acute GVHD

Results of multivariable Cox proportional hazards models evaluating CMV reactivation (any positive) as a risk factor for development of acute GVHD by day 100 after allogeneic HCT.

	events	adjusted HR	95%CI	p value
Acute GVHD grade 2-4	2381	1.09	0.97-1.22	0.17

Cofactors: patient age, donor age, donor relation, cell type, gender match and CMV serostatus

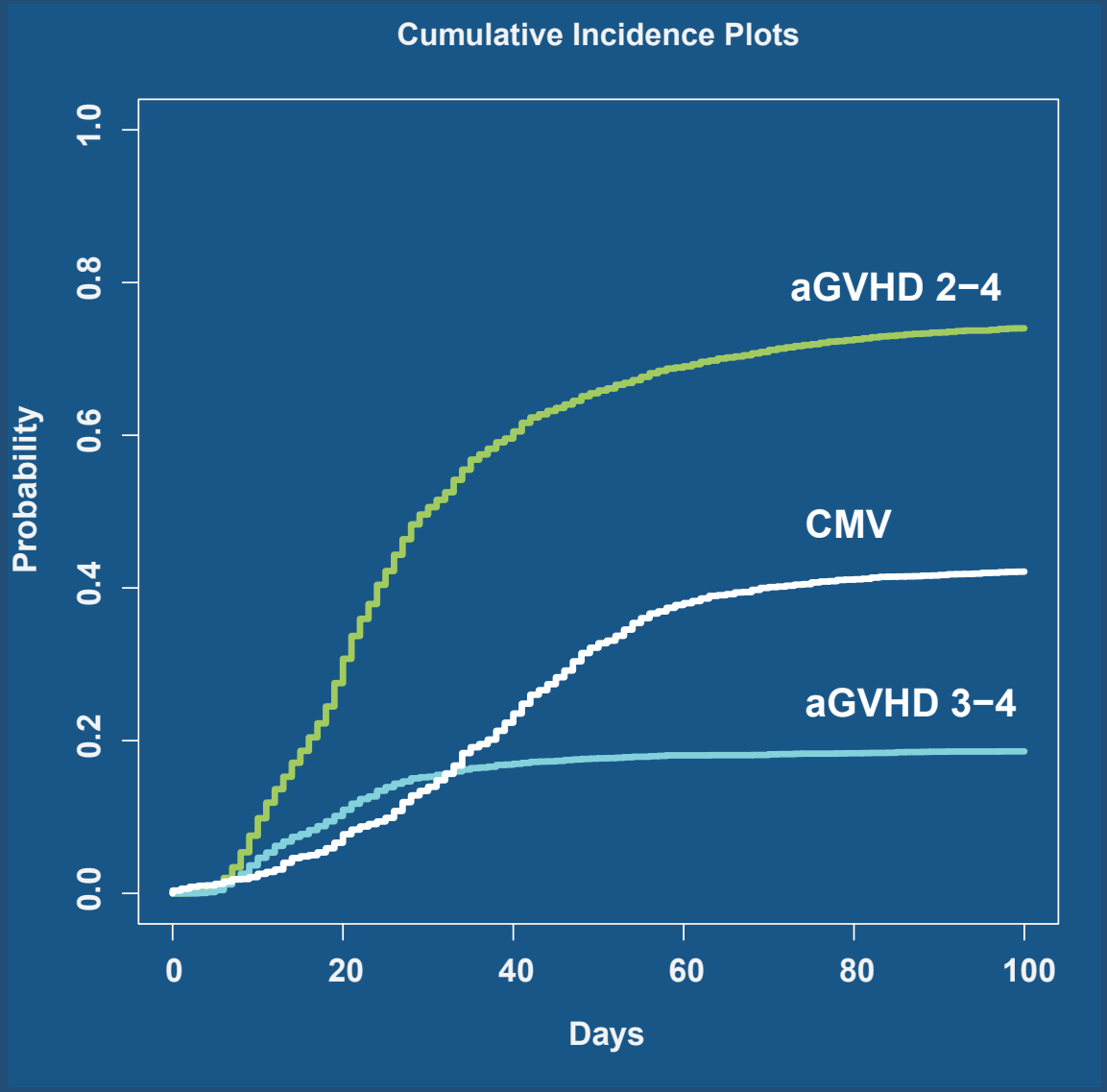
CMV viremia and acute GVHD

Results of multivariable Cox proportional hazards models evaluating CMV reactivation (any positive) as a risk factor for development of acute GVHD by day 100 after allogeneic HCT.

	events	adjusted HR	95%CI	p value
Acute GVHD grade 2-4	2381	1.09	0.97-1.22	0.17
Acute GVHD grade 3-4	681	0.91	0.68-1.21	0.50

Cofactors: patient age, donor age, donor relation, cell type, gender match and CMV serostatus

CMV viremia and acute GVHD



CMV viremia and Chronic GVHD

Results of multivariable Cox proportional hazards models evaluating CMV reactivation (any positive) as a risk factor for development of NIH chronic GVHD by 1 year after allogeneic HCT.

	events	adjusted HR	95%CI	p value
Any CMV reactivation	1015	0.94	0.8-1.1	0.34

Cofactors: patient age, donor age, donor relation, cell source, conditioning regimen, gender match, CMV serostatus, neutropenia, year of transplant, acute GVHD grade 2-4.

CMV viremia and chronic GVHD

Results of multivariable Cox proportional hazards models evaluating CMV reactivation (any positive) as a risk factor for development of NIH chronic GVHD by 1 year after allogeneic HCT.

	events	adjusted HR	95%CI	p value
Any CMV reactivation	1015	0.94	0.8-1.1	0.34
PCR> 250 IU or pp65>10		0.89	0.8-1.0	0.15
PCR>1000 IU or pp65>100		0.9	0.7-1.1	0.34

CMV viremia and infection

Results of multivariable Cox proportional hazards models evaluating CMV reactivation as a risk factor for bacteremia and invasive fungal infection by day 100 after HCT.

Any CMV reactivation	events	adjusted HR	95%CI	p value
Any bacteremia	1177	1.09	0.9-1.3	0.26
Gram positive bacteremia	422	1.26	1.0-1.6	0.08
Gram negative bacteremia	283	1.24	0.9-1.6	0.11
Invasive fungal infection	**392**	**1.52**	**1.2-2.0**	**0.002**
Bacteremia or fungal infection	**1394**	**1.19**	**1.0-1.4**	**0.013**

Cofactors: patient age, donor age, donor relation/HLA, cell source, gender match, CMV serostatus, neutropenia, year of transplant and acute GVHD grade 2-4.

Subgroup analysis

CMV + patients, monitored by PCR (2007-2013), n=704

	events	adjusted HR	95%CI	p value
Invasive fungal infection	76			
Any CMV reactivation		1.12	0.6-2.0	0.69

Cofactors: patient age, cell source, gender match, conditioning regimen, gender match, donor CMV, neutropenia, acute GVHD grade 2-4, and mold-active antifungal treatment

Subgroup analysis

CMV + patients, monitored by PCR (2007-2013), n=704

	events	adjusted HR	95%CI	p value
Invasive fungal infection	76			
Any CMV reactivation		1.12	0.6-2.0	0.69
PCR > 1000 IU/ml		1.91	1.0-3.5	0.04

Cofactors: patient age, cell source, gender match, conditioning regimen, gender match, donor CMV, neutropenia, acute GVHD grade 2-4, and mold-active antifungal treatment

Conclusions

- CMV reactivation was not associated with GVHD
  - Acute GVHD develops prior to CMV viremia
- Our analyses confirm that CMV reactivation is associated with increased risk (HR 1.5) of invasive fungal infections, independent of treatment-associated neutropenia.
- Consideration of these infectious indirect effects of CMV infection as components of a composite endpoint in clinical trials would be reasonable.

Limitations

- Dataset does not contain dates of acute GVHD progression
- Analyzing infections only through day 100 may underestimate the risk
- Increased use of mold-active prophylaxis may decrease incidence of IFI

Thank you

CMV viremia and infection

Moderate viral load (antigenemia >10 positive cells or PCR >250 IU/ml)				
	events	**adjusted HR**	**95%CI**	**p value**
Any bacteremia	1177	1.1	0.9-1.3	0.36
Gram positive bacteremia	422	1.23	0.9-1.7	0.18
Gram negative bacteremia	283	1.3	1.0-1.8	0.1
Invasive fungal infection	**392**	**1.57**	**1.1-2.2**	**0.009**
Bacteremia or fungal infection	**1394**	**1.26**	**1.1-1.5**	**0.012**

CMV viremia and infection

High viral load (antigenemia >100 positive cells or PCR >1000 IU/ml)				
	events	**adjusted HR**	**95%CI**	**p value**
Any bacteremia	**1177**	**1.29**	**1.0-1.7**	**0.05**
Gram positive bacteremia	422	1.38	0.9-2.1	0.14
Gram negative bacteremia	**283**	**1.68**	**1.2-2.4**	**0.006**
Invasive fungal infection	392	1.32	0.8-2.1	0.26
Bacteremia or fungal infection	**1394**	**1.38**	**1.1-1.7**	**0.007**