Infectious complications after second allogeneic hematopoietic cell transplant (Allo-HCT) in adult patients with hematological malignancies

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Background

- 2nd Allo-HCT can be given for relapse of primary malignancy, development of a second hematologic malignancy, or failure to engraft
- Data regarding outcome and complications after a 2nd Allo-HCT are limited; most studies are in children, but use of this modality has increased in adults.
- We characterized the infectious complications and outcomes of adult patients who received a 2nd Allo-HCT in our two medical centers

Methods

- Retrospective chart review of 60 adults who received a 2nd Allo-HCT from 2010–2015 at two medical centers in SE Michigan
- Endpoints:
  - Occurrence/outcome infectious episodes over 2 years after 2nd Allo-HCT
  - 2-year overall mortality after 2nd Allo-HCT
  - Cause of death within 2 years after 2nd Allo-HCT
- Infectious episodes defined as fever/hemodynamic instability + antibiotic use
- Episodes were separated into 3 periods:

  pre-engraftment: <30d post Allo-HCT

  early post-engraftment: 30-100d post Allo-HCT

  late post-engraftment: >100d post Allo-HCT

Results

Features related to 1st Allo-HCT

Feature	n	%
Reason for 1st Allo-HCT		
Acute leukemia or myelodysplastic syndrome	44	73
Myelofibrosis	6	10
Lymphoma	5	8
Chronic leukemia	2	3
Aplastic anemia	2	3
Plasma cell dyscrasia	1	2
Age at 1st Allo-HCT, yr (mean ± std dev)	46.2 ± 14.1	
Time to engraftment after 1st Allo-HCT, days (mean ± std dev)		
Neutrophils	13 ± 4	
Platelets	24 ± 24	

Demographic features of 2nd Allo-HCT recipients, n=60

Feature	n	%
Female sex	24	40
Race		
White	48	80
Black	9	15
Asian	2	3
Not specified	1	2
Comorbid conditions		
Malignancy*	7	12
Diabetes mellitus	5	8
Autoimmune disease	3	5
Chronic kidney disease	2	3
Coronary artery disease	1	2
Chronic obstructive pulmonary disease	1	2
Transplant center		
Karmanos Cancer Institute	29	48
University of Michigan	31	52

* breast n=2, testicular n=1, skin n=1, prostate n=1, labia n=1, colon n=1

Transplant features of 2nd Allo-HCT recipients, n=60

	n	%
Reason for 2nd Allo-HCT		
Relapse of original malignancy	37	62
Acute graft failure	12	20
New malignancy (including treatment-related)	6	10
Chronic graft failure	4	7
No indication available	1	2
Conditioning regimen		
Fludarabine	43	72
Busulfan	27	45
Melphalan	13	22
Clofarabine	10	17
Cytarabine	8	13
Rituximab	2	3
Total lymphoid irradiation	30	50
Anti-thymocyte globulin	19	32
Reduced intensity conditioning	14	23
Time from first to second transplant, days (median, range)	344 (32-8248)	
Engraftment		
Neutrophil engraftment occurred	50	83
Time to engraftment, days (mean ± std dev)	13 ± 4	
Platelet engraftment occurred	41	68
Time to engraftment, days (mean ± std dev)	23 ± 23	

- 183 infectious episodes occurred in 58 patients after 2nd Allo-HCT; only 2 patients developed no infections (one relapsed shortly after 2nd Allo-HCT and died; the other relapsed after one year and died)
- 75 episodes (41%) occurred <30 days post 2nd Allo-HCT
  - 39 (52%) were bacterial infections; C. *difficile* (n=7, 18%) and VRE (n=6, 15%) most common
- 56 episodes (31%) occurred 30–100d post 2nd Allo-HCT
  - 25 (45%) of infections were viral; CMV (n=11, 44%) and BK virus (n=6, 24%) most common
- 52 episodes (28%) occurred >100d post 2nd Allo-HCT
  - 23 (44%) were bacterial; coagulase (-) *Staphylococcus* (n=5, 22%) and VRE (n=3, 13%) most common

Bacterial infections occurring after 2nd Allo-HCT

Pathogen	Infection site	<30 days	>30-100 days	>100 days
Coagulase negative *Staphylococcus*	Bacteremia	2	1	5
Vancomycin resistant *Enterococcus*	Bacteremia	6	2	3
	UTI	1	0	1
Clostridioides difficile	Colitis	7	6	2
Pseudomonas species	Bacteremia	1	2	1
	UTI	0	1	0
	Pneumonia	1	1	2
Methicillin resistant *Staphylococcus aureus*	Bacteremia	1	0	0
	Respiratory	1	0	1
Vancomycin susceptible *Enterococcus*	Bacteremia	3	1	1
	UTI	2	1	0
Enterobacteriaceae	Bacteremia	3	1	2
	UTI	0	3	1
Other*	Bacteremia	4	2	1

*includes *Achromobacter* (1), *Corynebacterium* (1), *Stenotrophomonas* (1), *Streptoccoccus* (4)

Viral infections occurring after 2nd Allo-HCT

Pathogen	Infection site	<30 days	>30-100 days	>100 days
CMV	Viremia	7	10	3
	Colitis	1	2	0
HHV-6	Viremia	2	2	0
HSV	Cutaneous	4	0	0
Respiratory viruses*	Respiratory	0	2	9
BK Virus	Urinary tract	4	6	0
EBV	Viremia	1	2	1
VZV	Skin	0	1	4

* includes enterovirus, human metapneumovirus, influenza A, parainfluenza, rhinovirus, and RSV

Fungal infections occurring after 2nd Allo-HCT

Pathogen	Infection site	<30 days	>30-100 days	>100 days
Aspergillus species	Pulmonary	1	2	1
	Disseminated	0	0	1
Alternaria species	Skin	1	0	0
	Sinus	1	0	0
Candida glabrata	Fungemia	1	2	0
Candida parapsilosis	Fungemia	1	0	0
Fusarium species	Skin	1	0	0
Pneumocystis jirovecii	Pulmonary	0	0	1
Rhizopus species	Disseminated	0	0	1
	Pulmonary	0	0	1

Mortality

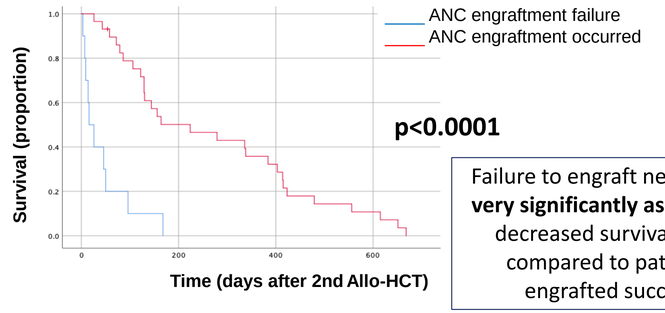
- **Overall mortality after 2nd Allo-HCT:**
- 27 patients (45%) died within 1 year
- 39 patients (65%) died within 2 years

- **Cause of death:**
- Infection: 16 deaths
- Hematology-related (relapse, graft failure, GVHD, VO): 16 deaths
- Other causes: 7 deaths (MI, subdural hematoma, alveolar hemorrhage, and several with unknown cause)

- **Deaths by period:**
- <30d: 5 infection-related vs1 hematology-related (p=0.05)
- >30<100d: 2 infection-related vs 6 hematology-related (p<0.001)

	<30 d	>30-<100d	>100d-1 yr	1 yr-2 yr
Total deaths	**7**	**9**	**11**	**12**
Infection-related deaths	**5**	**2**	**5**	**4**
Bacterial	4	1	3	2
Viral	1	1	0	0
Fungal	0	0	4	2
Hematology-related deaths	**1**	**6**	**5**	**4**
Relapse	0	3	5	3
Graft failure	1	2	0	0
GVHD	0	0	0	1
VOD	0	1	0	0
Other (non-Heme/non-ID)	**1**	**2**	**1**	**4**

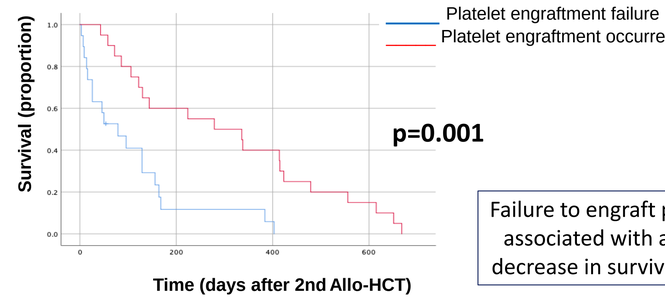
ANC engraftment and survival



p<0.0001

Failure to engraft neutrophils was **very significantly associated** with decreased survival over time compared to patients who engrafted successfully.

Platelet engraftment and survival



p=0.001

Failure to engraft platelets was associated with a significant decrease in survival over time.

Conclusions

- All but 2 patients receiving a 2nd allo-HCT experienced at least one infectious episode
- Infections were most frequent in the first 30 days following a 2nd Allo-HCT
- Most infection-related deaths occurred >100 days after 2nd Allo-HCT
- Failure to engraft and delayed engraftment of platelets and neutrophils was associated with decreased survival and likely contributed to the high number of infections in patients receiving a 2nd Allo-HCT

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