De-escalation of Broad Spectrum Antibiotics during Cytokine Release Syndrome with Haploidentical Hematopoietic Stem Cell Transplantation

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Background

- Fever is a common component of cytokine release syndrome (CRS) occurring in 90% of patients undergoing haploidentical hematopoietic stem cell transplantation (Haplo-HSCT). [1]
- Fevers typically occur between the stem cell infusion (Day 0) and initiation of post-transplant cyclophosphamide and are often confused with febrile neutropenia (FN).
- Due to longer time to engraftment in Haplo-HSCT, CRS/FN exposes patients to prolonged courses of empiric broad spectrum antibiotic (BSA) therapy increasing the risk for multi-drug resistant organisms.
- A small cohort of Haplo-HSCT patients among a larger de-escalation study observed significant reductions in BSA duration of therapy when using an early de-escalation approach (p = 0.006).[2]
- At Yale New Haven Health (YNHH), our practice has recently changed to recommend antibiotic de-escalation to prophylaxis after 7 days of BSA if no infection is identified regardless of fever.

Objectives

Primary Endpoint:

- Assess the incidence of breakthrough infections with the new de-escalation recommendations of BSA in patients who develop CRS/FN

Secondary Endpoints:

- Rate of FN, rate of de-escalation, rate of recurrent fevers, duration of BSA, and positive blood culture data

Methods

- A single center, retrospective chart review of adult haploidentical HSCT patients at YNHH between July 2016 and February 2020 who developed CRS/FN between Day 0 and Day +5 was conducted utilizing the electronic medical record.
- Bacteremia was defined using NHSN definitions.[3]

Exclusion Criteria

- Hospitalization greater than 30 days
- Engraftment failure
- Deceased prior to neutrophil recovery

Patient Selection

Patients who underwent a Haplo-HSCT between July 2016 – February 2020
N = 52

Excluded Patients, (10)
- Prolonged hospitalization due to non-infectious complications (5)
- Never developed FN between Day 0 and +5 (4)
- Deceased prior to neutropenic recovery (1)

Included Patients, n = 42
Included Haplo-HSCT, y = 43

- Negative blood cultures n = 39 (91%)
- Bacteremia n = 4 (9%)

Results

Table 1: Patient Characteristics

Baseline Demographics	n = 42
Age, median (range)	54 (24 -77)
Male, n (%)	30 (71)
Primary Diagnosis, n (%)	
Acute myeloid leukemia	17 (40)
Acute lymphocytic leukemia	9 (21)
Non Hodgkin Lymphoma	8 (19)
Myelodysplastic Syndrome	3 (7)
CLL	2 (5)
Hodgkins Lymphoma	2 (5)
Other	1 (2)
Type of Conditioning Regimen, n (%)	
Reduced intensity	25 (59)
Myeloablative	18 (42)
Type of Donor Match, n (%)	
Matched related donor, 5/10	21 (72)
Matched related donor, 6/10	10 (23)
Matched related donor, 7/10	2 (5)
Type of Antibacterial Prophylaxis, n (%)	
Moxifloxacin	41 (95)
Fosfomycin	2 (5)

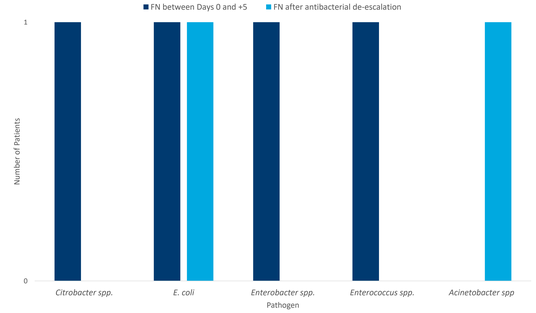
Results

Table 2: Negative Blood Culture Associated with CRS Fever

	Haplo-HSCT with negative blood cultures y = 39
De-escalated back to antibacterial prophylaxis, n (%)	**26 (67)**
Duration of BSA, median days (range)	7 (5-24)*
Recurrent fever incidence post de-escalation, n, (%)	7 (27)
Recurrent fever onset, median days, (range)	4, (2-14)
Subsequent positive blood culture after de-escalation, n, (%)	2 (8)
Fever with bacterial infection within 30 days post neutrophil recovery	0
Total duration of neutropenia, median days, (range)	15 (6-31)
Remained on BSA until neutrophil recovery, n (%)	**13 (33)**
Duration of BSA, median days (range)	17 (13-21)*
Total duration of neutropenia, median days, (range)	17 (9-42)
Breakthrough infections	0

***p-value = <0.001**

Figure 1: Culture Documented Breakthrough Organisms



Discussion

- Among Haplo-HSCT patients with CRS fevers between day 0 and day +5, there is a low rate of positive blood cultures at 9%.
- Two-thirds of patients with negative cultures after a febrile episode were able to be de-escalated back to antibacterial prophylaxis.
- In patients who were de-escalated back to prophylaxis, the majority of recurrent fevers were not attributed to breakthrough bacteremia.
- De-escalating antibiotics in patients with fevers due to CRS allows for a statistically significant reduction in BSA exposure when compared to patients who were not de-escalated.
- Of the 26 patients who were de-escalated back to antibacterial prophylaxis, there was a 0% incidence of mortality .
- Although it was not assessed in this study, other potential benefits of de-escalating BSA is decreased risk for resistance and *Clostridioides difficile* infection (CDI). Further studies are warranted to assess these additional benefits.

Conclusion

De-escalation of BSA in FN/CRS in Haplo-HSCT patients can be safely accomplished with low rates of breakthrough bacteremia. In addition, de-escalation allows for the reduced duration of unnecessary, prolonged antibiotic exposure and potentially lessens the risk for selection of resistant pathogens and CDI.

References

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