Risks versus Benefits of Metronidazole Use for the Prevention of Acute GVHD in Allogeneic Stem Cell Transplant Recipients

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BACKGROUND

- Approximately 40% of allogeneic hematopoietic stem cell transplant (HSCT) patients develop acute graft versus host disease (aGVHD) which is associated with mortality rates of 16-50%.[1, 2, 3]
- To reduce the risk of aGVHD, methods such as gut bacterial decontamination with antibiotics such as metronidazole have been studied since the 1970s.[4, 5]
- Recently, conflicting studies have shown the loss of bacterial diversity due to antibiotic treatment can increase GVHD-related mortality. Given the lack of strong clinical evidence, guidelines do not support the practice of metronidazole prophylaxis for aGVHD.[6, 7]
- GVHD prophylaxis varies among different institutions.
- A current practice at our institution is to prescribe patients with metronidazole for the first 35 days after transplantation in order to reduce risk of aGVHD.

OBJECTIVES

- Evaluate the incidence of aGVHD in patients who received metronidazole prophylaxis versus patients who did not receive metronidazole prophylaxis
- Determine the frequency of metronidazole-related adverse effects, rates of metronidazole discontinuation, incidence of *Clostridioides difficile* infection, mortality, and overall survival

METHODS

Study Design: Retrospective, single-center study conducted at an academic medical institution consisting of 460 beds

Eligibility	
Inclusion Criteria	• Adults ≥ 18 years • Patients who received an allogeneic HSCT performed at UTSW between 01/01/2010 – 12/31/2013
Exclusion Criteria	• Patients with a documented metronidazole allergy • Patients with preceding allogeneic HSCT • Received metronidazole for an indication outside of aGVHD prophylaxis

Study Endpoints	
Primary Endpoint	• Incidence of aGVHD
Secondary Endpoints	• Frequency of metronidazole-related adverse effects • Rate of metronidazole discontinuation due to intolerance • Incidence of *C. difficile* infection • Mortality (GVHD-related and non-GVHD-related) • Overall survival (100-day and 1-year)

RESULTS

PRELIMINARY DATA

Figure 1. Flow diagram of study population

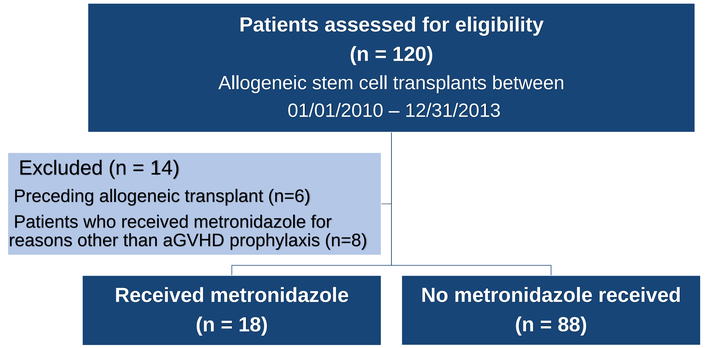

Table 1. Baseline demographics

Characteristics	No metronidazole (n = 18)	Metronidazole (n = 88)	P-value
Age at transplantation, as years, median (range)	56 (22 – 69)	56 (19 – 72)	--
Gender			0.91
Male	11 (61.1%)	55 (62.5%)	--
Female	7 (38.9%)	33 (37.5%)	--
Conditioning regimen			0.34
Myeloablative	10 (55.6%)	38 (43.2%)	--
Non-myeloablative	8 (44.4%)	50 (56.8%)	--
Donor type			0.43
Related	8 (44.4%)	49 (53.1%)	--
Haploidentical	0 (0%)	3 (3.1%)	--
Unrelated	10 (55.6%)	36 (43.8%)	--
Graft source			0.31
Peripheral blood	17 (94.4%)	87 (98.9%)	--
Bone marrow	1 (5.5%)	1 (1.1%)	--

Table 2. Primary outcome

Results	No metronidazole (n = 18)	Metronidazole (n = 88)	P-value
GVHD (acute or chronic)	13 (72.2%)	61 (69.3%)	0.81
Acute GVHD	11 (61.1%)	45 (51.1%)	0.44
- Liver	1 (5.6%)	9 (10.2%)	1.00
- Skin	9 (50.0%)	38 (43.1%)	0.60
- Gastrointestinal	9 (50.0%)	23 (26.1%)	**0.045**

RESULTS (continued)

Table 3. Secondary outcomes

Results	Incidence from Literature	Metronidazole (n = 88)
Metronidazole-related adverse effects	--	22 (25.0%)
Headache	18%	0 (0%)
Gastrointestinal	12%	17 (19.3%)
Metallic taste	9%	3 (3.4%)
Central neurotoxicity	33%	0 (0%)
Neuropathy	1.7 – 17.9%	0 (0%)
Infection	3 – 7 %	0 (0%)
Other adverse effect	Undefined	3 (3.4%)
Metronidazole discontinuation due to intolerance	--	20 (22.7%)
Metronidazole duration, as days, median (range)	--	32.5 (1-50)

Results	No metronidazole (n = 18)	Metronidazole (n = 88)	P-value
C. Difficile infection	1 (5.6%)	7 (7.3%)	1.00
Mortality – GVHD-related			0.90
GVHD-related	2 (11.8%)	15 (88.2%)	--
Not GVHD-related	8 (20.0%)	32 (80.0%)	--
Unknown	1 (16.7%)	5 (83.3%)	--
Still alive	7 (16.3%)	36 (83.7%)	--
Overall survival			--
100 day	17 (17.9%)	78 (82.1%)	0.69
1 year	12 (15.8%)	64 (84.2%)	0.60

CONCLUSIONS

- These results show a difference in the incidence of gastrointestinal aGVHD, with a higher incidence of aGVHD observed in patients who did not receive metronidazole.
- However, the risks versus benefits of using metronidazole must be considered because 25% of patients experienced an adverse effect, mainly gastrointestinal.
- The standard of care for aGVHD prophylaxis has since changed from the time of this study to include cyclophosphamide for GVHD prophylaxis. Future studies evaluating aGVHD with metronidazole with cyclophosphamide versus metronidazole alone are needed to assess if metronidazole has any added benefit.

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DISCLOSURE

The authors of this poster have no financial disclosures or conflicts of interest to report.