Infection patterns and outcomes in patients with newly diagnosed multiple myeloma: Preliminary results from the IMPROVE (Immunoglobulins in myeloma patients: research into outcomes, variation in practice and epidemiology) Cohort Study

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Introduction

- Infections are an important cause of morbidity and mortality in patients with multiple myeloma (MM).
- Immunoglobulin (Ig) therapy is often used to prevent or treat infections in MM patients.
- Ig therapy is in limited supply and very expensive: Australia spends approximately $100 million annually on Ig products for patients with haematological malignancies alone.[1]
- The IMPROVE project aims to collect 'real world', up-to-date information on Ig use to guide policy and clinical practice. Results will be important to improve infection care for patients with MM and to improve stewardship of the national blood supply.

Objectives

- First analysis of baseline characteristics and infections in patients with newly diagnosed MM (NDMM) from the IMPROVE prospective cohort study.

Methods

Study design

- Prospective cohort study of infection prophylaxis, type and outcomes in NDMM patients.
- Sub-study of the Myeloma and Related Diseases Registry (MRDR), which has prospectively recruited >4000 patients from 50+ sites across Australia/New Zealand.
- The MRDR is a partnership between clinicians, participating hospitals and patients, and managed by the School of Public Health and Preventive Medicine at Monash University in Melbourne, Australia.

Data collection

- Data were accessed from the MRDR, with additional data on infection, prophylaxis, types and outcomes collected using a dedicated IMPROVE case report form (See Table 1).

Table 1: Data collection

Diagnosis	Disease	Treatment	Outcomes	IMPROVE-specific
Patient demographics	Disease type	Drug/dose of MM treatment	Progression-free survival	Immunoglobulin treatment
Co-morbidities	Stage	Number of lines of MM therapy	Overall survival	Infection prophylaxis and types
Performance status	Specific risk scores	Reasons for changing/ discontinuation		Infection treatment and complications
	Laboratory diagnostic data			Infection outcomes

Statistical analysis: All statistical analyses were performed using Stata 16.1 statistical package (Stata Corp, College Station, Texas).

Results

Study population

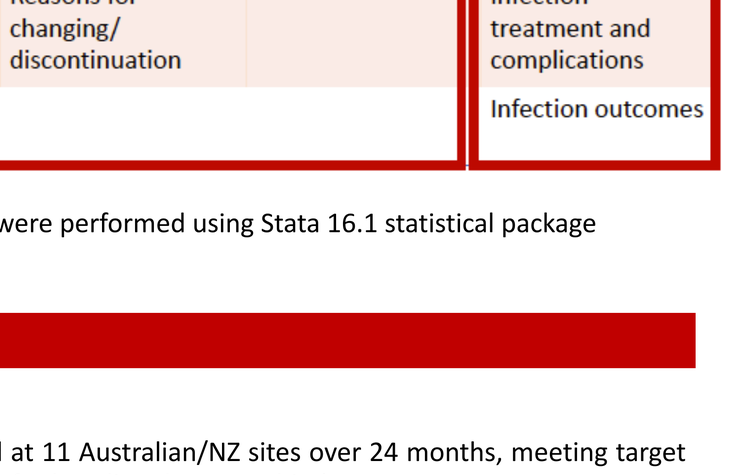
- 307 NDMM patients have been enrolled at 11 Australian/NZ sites over 24 months, meeting target recruitment of 300 patients. (See Table 2 for baseline demographics)
- To date, 217 (71%) of all recruited patients have reached the final 16-month follow-up timepoint. Final follow-up for all patients will be reached in mid-2021.

Table 2: Baseline patient demographics, 307 participants

Characteristic	Number (%)
Age in years, median (IQR)	67.6 (59.5, 73.8)
Male sex	192 (62.5%)
International staging system (ISS) score	
1	53/224 (23.7%)
2	96/224 (42.9%)
3	75/224 (33.5%)
Missing baseline values	83
Eastern Cooperative Oncology Group (ECOG) performance status ≥2	49 (16.0%)
Comorbidities	
Moderate to severe cardiac disease	48 (15.6%)
Moderate to severe pulmonary disease	26 (8.5%)
Diabetes requiring medication	42 (13.7%)
Liver disease	6 (2.0%)
Peripheral neuropathy	6 (2.0%)
Chronic kidney disease	26 (8.5%)
Induction therapy	290 (94.5%)
Bortezomib-based	241 (78.5%)
Lenalidomide-based	37 (12.1%)
Includes dexamethasone	289 (94.1%)
Autograft	152 (49.5%)
Presence of hypogammaglobulinaemia	
Hypogammaglobulinaemia (IgG<7g/L)	74/190 (38.9%)
Severe hypogammaglobulinaemia (IgG<4g/L)	36/190 (18.9%)
Missing baseline values	117
Deaths	54 (17.6%)

Incidence and severity of infections

- 466 infection episodes have been detected in 209 patients (2.2 infections/patient) over 4280 months (1.31 per patient-year).
- 133 (43.3%) patients had at least 1 major ≥ Grade 3 infection and 209 (68.1%) patients had ≥ 1 infection of any grade (See Figure 1).
- Median time to first major infection was 138 days (IQR 52-231) (see Figure 2).
- Ig therapy was reported to be administered to only 28 patients (9.1%).



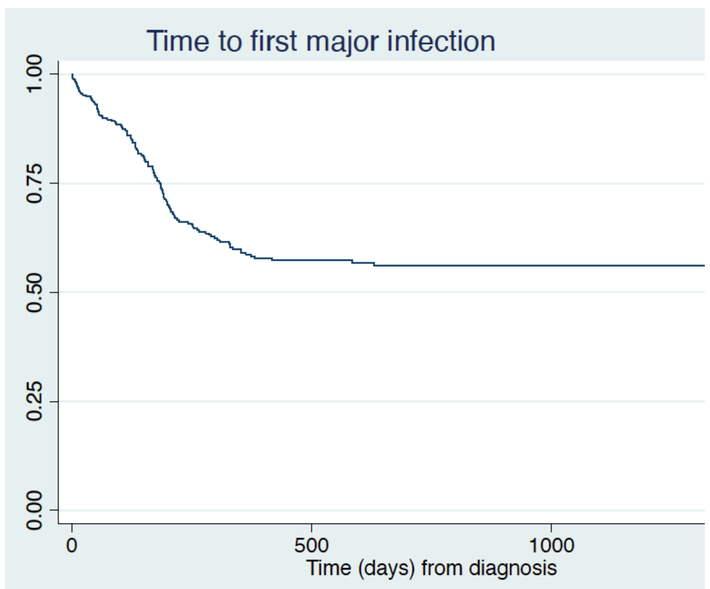
Syndromes of infection

- The type and frequency of infections are outlined in Table 3.
- The most common infection sites were respiratory (32.1%) or urogenital (10.1%).

Table 3: Type and frequency of infections

Type of infection	N=466 Number of infection episodes (%)
Respiratory	149 (32.0%)
Urogenital	47 (10.1%)
Blood-borne	33 (7.1%)
Haematologic/Lymphatic	29 (6.2%)
Gastrointestinal	28 (6.0%)
Skin	21 (4.5%)
Eyes	19 (4.1%)
Ear/Nose/Throat	14 (3.0%)
Cardiovascular	2 (0.4%)
Musculoskeletal	2 (0.4%)
Other	17 (3.6%)
Unknown	105 (22.5%)

Figure 2: Time to first major infection



Aetiology of infections

- The majority of episodes (71.2%) had no organisms identified.
- Table 4 details the causative organisms implicated in the 134 episodes of infection.
- Bacteria were the most common cause of infection.
- Escherichia coli was the most frequent bacteria isolated.
- Respiratory viruses caused 87.2% of all viral infections.
- There were no documented infections with SARS-CoV-2.

Table 4: Causative organisms in 134 episodes of infection where organisms were identified

Organism	N=134 Number (%)
Gram negative	56 (41.8%)
E. coli	18
Klebsiella pneumoniae	8
Pseudomonas aeruginosa	5
Enterobacter cloacae	3
Others	11
Gram positive	36 (26.9%)
Staphylococcus aureus	7
Coagulase negative Staphylococcus	7
Streptococcus pneumoniae	5
Enterococcus spp.	4
Clostridium difficile	3
Others	5
Mixed organisms*	17 (12.7%)
Viruses	39 (29.1%)
*Respiratory viruses***	34 (25.4%)
Herpes simplex virus (HSV-1 or HSV-2)	4
Enterovirus	1
Fungi	2 (1.5%)
Candida spp.	1
Aspergillus spp.	1

* More than one organism identified.
** Implicated in respiratory viruses: Rhinovirus (9); respiratory syncytial virus (8); influenza A (7); parainfluenza virus (3); human metapneumovirus (3); picornavirus (2); adenovirus (2).

Clinical outcomes

- Overall survival was 82.4% (253/307).
- Of 54 deaths, 5 (9.2%) were reported as caused by infection - 2 blood-borne infection types (caused by *Clostridium septicum*, methicillin-resistant *Staphylococcus aureus*), 2 mixed infection types (*Klebsiella pneumoniae* and *Streptococcus salivarius, Pseudomonas aeruginosa* and *S. lugdunesis*) and one unknown infection type.

Conclusions

- Preliminary results from the 'real-world' IMPROVE study show that after median follow-up of 16 months, infections are frequent in NDMM patients.
- Further analysis of immunoglobulin and other prophylaxis measures and infection risk-factors is in progress and will be presented separately.
- Improved prevention and surveillance strategies especially targeted to the first 150 days are urgently required to improve infection outcomes for NDMM patients.
- A parallel study in chronic lymphocytic leukaemia/Non-Hodgkin lymphoma (the ICAN study) is underway.

References

1. MSAC Assessment report. *Immunoglobulin for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation, 2019.*

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