Using Data Science to Characterize Patterns in Cardiovascular Clinical Data: Topological Analysis of Baseline Characteristics in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Enrolled in Carfilzomib Trials

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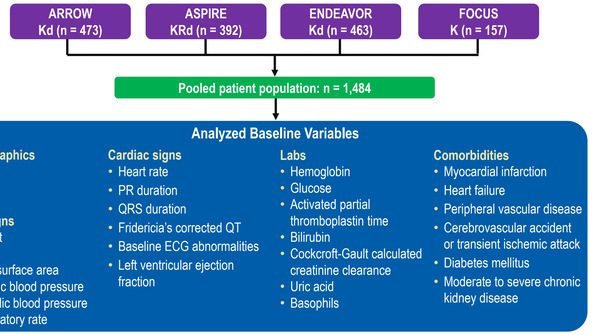
BACKGROUND

- Patients with multiple myeloma (MM) are often elderly and have cardiovascular risk factors and/or established cardiovascular disease[1,2]
  - The median age at diagnosis of MM is ~69 years[1]
  - Retrospective claims analysis showed that 63% of patients with newly diagnosed MM (n = 22,076) had a cardiovascular comorbidity at baseline, with arrhythmias and ischemic heart disease being most common[2]
- Carfilzomib is a second-generation proteasome inhibitor that is approved in combination with dexamethasone (Kd) alone, and also with lenalidomide plus dexamethasone (KRd), daratumumab plus dexamethasone (KdD), and isatuximab plus dexamethasone for adult patients with relapsed/refractory (RR) MM[3,4]
- Oncology clinical trials amass extensive amounts of patient data, which provides the opportunity to leverage machine learning
- The objective of this study was to use topological analysis to identify characteristics at baseline associated with subsequent cardiovascular adverse events (AEs) in patients with RRMM enrolled in carfilzomib trials

METHODS

- Data from the investigational arm (carfilzomib-treatment) of four phase 3 clinical trials (ARROW [NCT02412878], ASPIRE [NCT01080391], FOCUS [NCT01302392], and ENDEAVOR [NCT01568866]) were pooled retrospectively for this post hoc exploratory analysis
- Analyzed variables are shown in **Figure 1**
  - No post-baseline data were included
- Treatment-emergent AEs of interest were grade ≥ 3 cardiac failure, ischemic heart disease, and hypertension
- Topological data analysis was used to reveal AE occurrence micropatterns
  - Analytic approach akin to dimensionality reduction and distinct from traditional multivariate modeling analysis
- For each AE of interest, risk profiles were generated by portioning the population into groups with higher-risk (Group H) and lower-risk (Group L) of AEs by posterior probability. Preformulated requirements for these groups were:
  - Size of Group H is ≤ double the size of AE population
  - AE incidence rate in Group H is ≥ double the overall rate
  - AE incidence rate in Group L is ≤ half the overall rate
  - Group H comprises ≥ two-third of AE occurrences, or equivalent
- Each continuous variable was converted into multiple binary variables to reflect clinically interpretable thresholds, and each categorical variable was one-hot encoded
- The higher-risk group H and the lower-risk group L were built up from the empty set and down from the full set, respectively
- The algorithm iteratively adds risk factors that define group H by jointly maximizing the posterior and prior AE probabilities, while optimally satisfying the above four conditions

Figure 1



RESULTS

Cardiac Failure

Figure 2. Topological Model of Baseline Characteristics Predicting Grade ≥ 3 Cardiac Failure

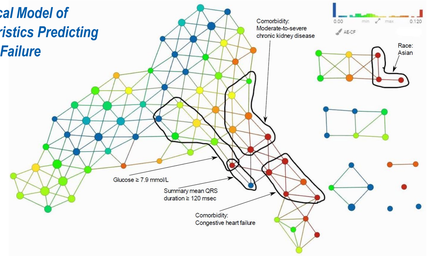


Table 1. Risk Factors for Grade ≥ 3 Cardiac Failure

Group	n_{Grp}	$p_{Grp,All}$ (%)	$n_{AE,Grp}$	$p_{AE,Grp}$ (%)	$p_{Grp,AE}$ (%)
Comorbidity: congestive heart failure	90	6.1	18	20.0	24.0
Comorbidity: moderate-to-severe CKD	134	9.0	15	11.2	20.0
Summary mean QRS duration ≥ 120 msec	99	6.7	15	15.2	20.0
Glucose ≥ 7.9 mmol/L	146	9.8	16	11.0	21.3
Race: Asian	102	6.9	11	10.8	14.7
Group H: any of the above	462	31.1	50	10.8	66.7
Group L: none of the above	1,022	68.9	25	2.4	33.3
All patients	1,484		75	5.1	

CKD, chronic kidney disease; $n_{AE,Grp}$, number of adverse-event patients in designated group; n_{Grp}, number of patients in designated group; $p_{AE,Grp}$, proportion of adverse-event patients in designated group; $p_{Grp,AE}$, proportion of designated-group patients among adverse-event patients; $p_{Grp,All}$, proportion of designated-group patients among all patients.

- Grade ≥ 3 cardiac failure occurred in 5.1% (75/1,484) of patients
- Cardiac failure AE rate was 4x higher in the high-risk group than in the low-risk group [10.8% vs 2.4%]
- Risk factors for grade ≥ 3 cardiac failure were baseline comorbidity of congestive heart failure or moderate-to-severe chronic kidney disease, mean QRS ≥ 120 msec, glucose ≥ 7.9 mmol/L, and Asian race

Ischemic Heart Disease

Figure 3. Topological Model of Baseline Characteristics Predicting Grade ≥ 3 Ischemic Heart Disease

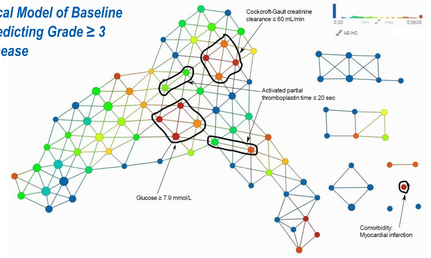


Table 2. Risk Factors for Grade ≥ 3 Ischemic Heart Disease

Group	n_{Grp}	$p_{Grp,All}$ (%)	$n_{AE,Grp}$	$p_{AE,Grp}$ (%)	$p_{Grp,AE}$ (%)
Comorbidity: myocardial infarction	26	1.8	5	19.2	15.2
Glucose ≥ 7.9 mmol/L	146	9.8	11	7.5	33.3
aPTT ≤ 20 sec	28	1.9	3	10.7	9.1
Cockcroft-Gault CrCl ≤ 60 mL/min	447	30.1	18	4.0	54.5
Group H: any of the above	571	38.5	24	4.2	72.7
Group L: none of the above	913	61.5	9	1.0	27.3
All patients	1,484		33	2.2	

aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; $n_{AE,Grp}$, number of adverse-event patients in designated group; n_{Grp}, number of patients in designated group; $p_{AE,Grp}$, proportion of adverse-event patients in designated group; $p_{Grp,AE}$, proportion of designated-group patients among adverse-event patients; $p_{Grp,All}$, proportion of designated-group patients among all patients.

- Grade ≥ 3 ischemic heart disease occurred in 2.2% (33/1,484) of patients
- Ischemic heart disease AE rate was 4x higher in the high-risk group than in the low-risk group [4.2% vs 1.0%]
- Risk factors for grade ≥ 3 ischemic heart disease were comorbidity of prior myocardial infarction, glucose ≥ 7.9 mmol/L, activated partial thromboplastin time (aPTT) ≤ 20 seconds, and creatinine clearance (CrCl) ≤ 60 mL/min

Hypertension

Figure 4. Topological Model of Baseline Characteristics Predicting Grade ≥ 3 Hypertension

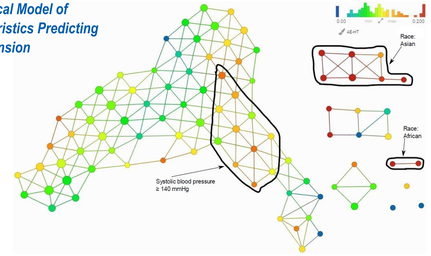


Table 3. Risk Factors for Grade ≥ 3 Hypertension

Group	n_{Grp}	$p_{Grp,All}$ (%)	$n_{AE,Grp}$	$p_{AE,Grp}$ (%)	$p_{Grp,AE}$ (%)
Systolic blood pressure ≥ 140 mmHg	375	25.3	59	15.7	43.4
Race: Asian	102	6.9	22	21.6	16.2
Race: African	22	1.5	4	18.2	2.9
Group H: any of the above	477	32.1	80	16.8	58.8
Group L: none of the above	1,007	67.9	56	5.6	41.2
All patients	1,484		136	9.2	

$n_{AE,Grp}$, number of adverse-event patients in designated group; n_{Grp}, number of patients in designated group; $p_{AE,Grp}$, proportion of adverse-event patients in designated group; $p_{Grp,AE}$, proportion of designated-group patients among adverse-event patients; $p_{Grp,All}$, proportion of designated-group patients among all patients.

- Grade ≥ 3 hypertension occurred in 9.2% (136/1,484) of patients
- Hypertension AE rate was 3x higher in the high-risk group than in the low-risk group [16.8% vs 5.6%]
- Risk factors for grade ≥ 3 hypertension were systolic blood pressure ≥ 140 mmHg and Asian or African race

CONCLUSIONS

- **This novel approach using topological analysis found that cardiovascular AEs in patients with RRMM clustered into small groups based on baseline characteristics**
- **Downstream analysis using binarized variables for built-in clinical interpretability and a fit-for-purpose iterative optimization algorithm found higher-risk groups characterized by known risk factors**
- **Characteristics associated with cardiovascular AEs were detectable by standard clinical assessment or laboratory tests**
- **Study limitations of this post hoc exploratory analysis include lack of comparator arm, small number of Asian patients (n=102), and that this novel methodology has not been validated in clinical settings**
- **These findings suggest that topological analysis may be a useful tool for leveraging machine learning in clinical trials**

DISCLOSURES

Hang Quach reports grants from Celgene, Amgen, GlaxoSmithKline, Karyopharm; consultancy and/or membership on an advisory committee from Takeda, GlaxoSmithKline, Karyopharm, Celgene, and Janssen; free drug for investigator-initiated study from Sanofi. **Heinz Ludwig** reports research funding from Amgen and Takeda; speakers bureau for Celgene, Janssen, Bristol Myers Squibb, Sanofi, and Amgen; advisory boards for Janssen, Bristol Myers Squibb, Sanofi, Amgen, and Seattle Genetics. **Ajai Chari** reports consultancy/advisory boards for Janssen, Celgene, Novartis, Amgen, Bristol Myers Squibb, Karyopharm, Sanofi Genzyme, Seattle Genetics, Oncopeptides, Millennium/Takeda, Antengene, GlaxoSmithKline, and Secura Bio; research funding from Janssen, Celgene, Novartis, Amgen, Pharmacyclics, Seattle Genetics, and Millennium/Takeda. **Joshua Richter** reports speakers bureau for Celgene and Janssen; consultancy/advisor for Celgene, Janssen, Karyopharm, Oncopeptides, Adaptive Biotechnologies, and Antengene. **Amanda Goldrick** reports employment with and stockholdings of Amgen. **Siddique Abbasi** reports employment with and stockholdings of Amgen. **Gilles Gnacadja** reports employment with and stockholdings of Amgen. **Joseph Mikhael** reports honoraria from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, Karyopharm, and Oncopeptides.

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