LETTER

MULTIPLE MYELOMA, GAMMOPATHIES

Changes in multiple myeloma treatment patterns during the early COVID-19 pandemic period

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TO THE EDITOR:

The COVID-19 pandemic has had dramatic impact on health maintenance and solid cancer screening [1], but its impact on the management of hematologic malignancies is less clear. We selected multiple myeloma (MM), the second most common hematologic malignancy, to evaluate potential changes in clinical presentation and treatment during the COVID-19 pandemic period (COVID). Early in the pandemic professional groups released guidance for changes in MM care, including recommendations to consider prolonging active surveillance, using all-oral regimens, and delaying autologous stem cell transplantation (ASCT) [2–7]. It is unknown whether patients presented with more advanced MM at diagnosis or experienced different patterns of MM treatment during COVID.

Our study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database containing patient-level data from ~280 community or academic cancer clinics across the US [8, 9], to examine adult MM patients who were newly diagnosed or treated from 2014 to 2020. The Institutional Review Board approved the study, including a waiver of informed consent.

We established two analytic cohorts: new patients (NEWPT $n = 1319$; 964 pre-COVID, 355 COVID) and established patients (ESTABLISHED $n = 2206$; 1014 pre-COVID, 1192 COVID). NEWPT included adults (age ≥ 18 years) newly diagnosed with MM during February–June in 2018 or 2019 (pre-COVID), or 2020 (COVID) with management (office visit, diagnostic testing, treatment) within 90 days after diagnosis. NEWPT were followed for 7 months from diagnosis, or until death, whichever came first. ESTABLISHED included adults receiving MM maintenance or a second or higher line of treatment (LOT) with an index date (start of treatment) of either 2/1/2017 (pre-COVID) or 2/1/2020 (COVID). To avoid overlap in the two periods, we selected patients diagnosed in 2014–2016 (pre-COVID) and 2017–2019 (COVID), followed to the end of observation year (2017 or 2020) or death, whichever came first.

Among NEWPT, we evaluated clinical presentation, Eastern Cooperative Oncology Group performance status (ECOG PS 0-1, 2–4, unknown), anemia/kidney function within 90 days prior to the diagnosis date, manually abstracted ISS stage, heavy/light chain and initial LOT. Time to treatment initiation (TTI) was measured as days from diagnosis to first therapy date. We evaluated receipt of ASCT, chemoimmunotherapy, supportive care (antiviral or bone modifying agents (BMA)). Treatments were grouped into LOTs using oncologist-defined, rule-based lines of therapy [10]. Study covariates included sex, age at diagnosis (≤64, 65–74, ≥75 years), race (White, Black/African American, Hispanic or Latino, other), insurance type, and academic versus community setting. For ESTABLISHED we examined chemoimmunotherapy used in each LOT, oral versus parenteral treatments, ASCT, and clinical trial participation.

We employed a pre-post design, comparing presentation and treatment during pre-COVID and COVID for both cohorts. Patient demographic, clinical characteristics, and treatments were compared between pre-COVID and COVID using Pearson's χ^2 test. We used Kaplan-Meier curves and log-rank tests to compare TTI between the two periods. Multivariable Cox proportional hazards regression was used to determine impact of COVID on TTI, with death as a competing risk, adjusting for sex, age, race, insurance type, stage, baseline ECOG PS, and hospital setting.

Most patients in both groups were non-Hispanic White; 80% were treated at community cancer clinics. For NEWPT, the median age at diagnosis was 71 (intra-quartile range (IQR) 62–77) years. We observed no differences in baseline stage, ECOG PS, or anemia/kidney function between the two periods (Table 1A). Among NEWPT, 878 (91.1%) pre-COVID and 306 (86.2%) COVID period patients received MM treatment. Compared with the pre-COVID, patients during COVID were less likely to initiate treatment ($p < 0.01$); and initiated treatment later (Fig. 1A), with a median TTI of 30 (95% confidence interval (CI) 29–32) and 32 (95% CI 29–34) days for pre-COVID and COVID, respectively ($p = 0.04$). After adjusting for patient demographic and clinical features, we observed a trend towards longer TTI during COVID (COVID vs pre-COVID hazard ratio = 0.88, 95% CI 0.77–1.01, $p = 0.06$; factors associated with TTI shown in Table 1B). More patients during COVID (80.4%) received IMID-regimens than their pre-COVID counterparts (74.3%, $p < 0.01$). Few in either period received

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Table 1. Baseline Patient Characteristics.

A. Baseline clinical features of newly diagnosed MM patients			
	Pre-COVID *n* **(%)**	**COVID** *n* **(%)**	***p***
Total	964	355	
ISS stage			
Stage I	223 (23.1)	68 (19.2)	0.28
Stage II	195 (20.2)	80 (22.5)	
Stage III	191 (19.8)	73 (20.6)	
Unknown	355 (36.8)	134 (37.7)	
ECOG			
0–1	228 (23.7)	75 (21.1)	0.96
2–4	34 (3.5)	11 (3.1)	
Unknown	702 (72.8)	269 (75.8)	
Hgb (g/L)			
4.9–9.9	264 (27.4)	89 (25.1)	0.43
10–17.4	99 (10.3)	40 (11.3)	
Unknown	601 (62.3)	226 (63.7)	
Creatinine (mg/dL)			
0.44–1.29	228 (23.6)	70 (19.7)	0.32
1.30–21.04	101 (10.5)	39 (11.0)	
Unknown	635 (65.9)	246 (69.3)	

B. Factors associated with time to initiate treatment			
	Hazard ratio	**95% Confidence interval**	***p***
Period			
Pre-COVID	1.00		
COVID	0.88	0.77–1.01	0.06
Gender			
Female	1.00		
Male	1.11	0.99–1.25	0.07
Age at diagnosis (years)			
37–64	1.00		
65–74	0.79	0.52–1.21	0.28
75–85	0.81	0.53–1.24	0.34
Race/ethnicity			
White	1.00		
Black	1.01	0.86–1.18	0.95
Hispanic	1.09	0.88–1.35	0.45
Other/unknown	0.77	0.66–0.90	<0.01
ISS stage			
Stage I	1.00		
Stage II	1.26	1.06–1.49	0.01
Stage III	1.53	1.28–1.81	<0.01
Unknown/not documented	0.89	0.77–1.04	0.16
Insurance			
Medicare	1.00		
Commercial	0.82	0.53–1.27	0.38
Other, include Medicaid	0.84	0.52–1.36	0.49
Uninsured/unknown	0.95	0.61–1.50	0.83

Table 1. continued

B. Factors associated with time to initiate treatment			
	Hazard ratio	**95% Confidence interval**	***p***
Practice type			
Community	1.00		
Academic	0.82	0.68–0.98	0.03
Baseline ECOG			
0–1	1.00		
2–4	0.87	0.60–1.28	0.48
Unknown	0.87	0.76–1.01	0.07

oral-only regimens (11.0% pre-COVID, 7.8% COVID, $p = 0.11$). Only 17.3% pre-COVID and 13.7% during COVID received more than one LOT during the observation period ($p = 0.14$). During pre-COVID 4.8% received monoclonal antibody (mAb), this increased to 14.4% during COVID ($p < 0.01$) (Fig. 1B). Among patients treated with proteasome inhibitors (PI), 69.0% pre-COVID and 75.2% COVID period patients received antivirals ($p = 0.06$). There was no difference in ASCT administration during the two periods (14.4% pre-COVID vs 13.4% COVID, $p = 0.68$).

ESTABLISHED patients had median age 69 (IQR 61–76). During COVID they received more mAb-regimens (28.9% vs 16.9%, $p < 0.01$) (Fig. 1C), and less cyclophosphamide (7.9% vs 15.1%, $p < 0.01$) compared with pre-COVID. Patients during pre-COVID were more likely to enroll in a clinical trial (3.3% vs 2.5%, $p = 0.03$). Oral-only regimens were used in 21.1% and 18.2% in pre-COVID and COVID, respectively ($p = 0.09$). The receipt of BMA was similar during the two periods for both cohorts: NEWPT 57.6% pre-COVID, 57.8% COVID, $p = 0.95$; ESTABLISHED 51.5% pre-COVID and 55.6% COVID; $p = 0.05$.

In summary, new MM patients during COVID were less likely to initiate treatment ($p < 0.01$) and trended towards a longer TTI after adjusting for patient characteristics. The increased frequency of frontline mAb-regimens in NEWPT during COVID likely reflects the influence of landmark publications on the success of novel quadruplet combinations and might not be attributable to the impact of the pandemic [11]. More patients during COVID received IMID-based regimen, reflecting overall less usage of alkylators in the modern era. Notwithstanding the obstacles of the pandemic, care continued for transplant eligible NEWPT within guidelines; they received appropriate chemoimmunotherapy regimens and ASCT during COVID. We demonstrate very low trial participation of MM patients even pre-COVID (3.3%) with further decrease during COVID, underscoring the need to enhance trial participation of MM patients.

While other studies have reported delayed/disrupted cancer screening and care during COVID [12–14], our study of real-world adult patients with MM in the US shows little evidence of delayed diagnosis or worsening of clinical presentation, and only modest changes in treatment early during the pandemic. One explanation for this difference is that clinical MM presentation often involves kidney failure, anemia, hypercalcemia, and pathologic bone fractures that must be addressed urgently. Further, the mainstay of MM treatment is systemic chemoimmunotherapy whereas solid tumors are often managed with surgery and/or chemoradiotherapy, which may have presented additional care coordination challenges. Our study is the first report describing patterns of care in MM during early pandemic and is consistent with a prior US study in metastatic cancers wherein the COVID-19 pandemic did not impact TTI or treatment selection [15].

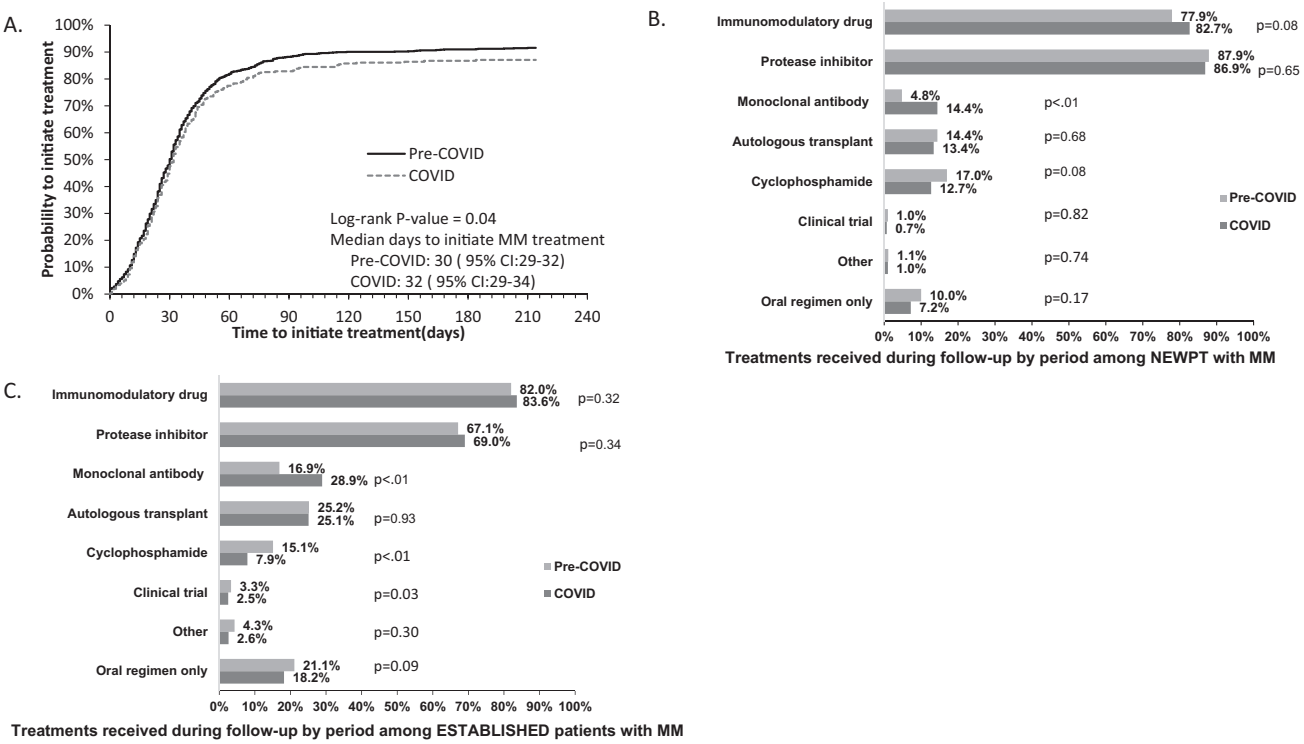

Fig. 1 Time to Treatment Initiation and Regimens. A Time to treatment initiation (TTI) in days among newly diagnosed patients with MM(NEWPT cohort); pre-COVID $n = 878$ and COVID $n = 306$. A trend toward longer TTI during COVID was observed. **B** Treatment regimens received among patients with newly diagnosed MM during the follow-up in pre-COVID and COVID periods. The use of mAb appeared to increase during COVID period. **C** Treatment regimens received during follow-up among ESTABLISHED patients with MM in pre-COVID and COVID periods. During COVID, patients received more mAb regimens and less cyclophosphamide compared with pre-COVID period.

Our study has notable limitations: the pre-post study design cannot address temporal changes in practice unrelated to COVID-19 pandemic, such as new drug approvals, including frontline use of mAbs. Flatiron Health EHR-derived de-identified database may not be fully representative of the entire population of patients with MM in the US across all oncology care settings. Given relatively small sample sizes, we could not test for heterogeneity across patients by race, ethnicity, age, or insurance. We lacked information on patient socioeconomic status and their access to technologies. Further, we focused on the early COVID-19 pandemic. It is plausible that additional practice changes occurred later during the pandemic. Nonetheless, our study captures the experience of a large cohort of MM patients during the early COVID-19 pandemic. Further studies are needed to examine potential effects of COVID-19 on clinical outcomes.

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AUTHOR CONTRIBUTIONS

NN, AJD, and SFH designed the study, performed research, and wrote the paper. RW performed research, analyzed data, and wrote paper. AMZ, NAP, RMS, and XM contributed to the study design, data analysis, and writing of the paper.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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