Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Leukemia Research 110 (2021) 106646

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

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Challenges of patients with myeloproliferative neoplasms (MPN) in times of COVID: First results from a patient survey by the German Study Group for MPN

Since 2020, the SARS−COV-2 Coronavirus pandemic has spread worldwide, with a substantial impact on global health care systems. According to the World Health Organization (WHO) Coronavirus Dash Board, there were 1,053,869 cases of COVID-19 infections confirmed and 16,248 COVID-19-related deaths in Germany until data cut off on November 30th 2020 [1]. Approximately 1.3 % of the German population had been infected with the virus in the first 10 months of the pandemic (with 83,190,556 inhabitants in Germany as reported by the Federal Statistical Office of Germany "Statistisches Bundesamt") [2]. As of data cut of in November 2020, 62,509,580 and 1,458,783 SARS-COV-2 infections and COVID-19 related deaths were confirmed worldwide, respectively [3].

Since the beginning of the pandemic, patient care in Germany has suffered considerably, either because patients were reluctant to personally see their physician due to fear of contraction of SARS-COV-2 or because hospitals postponed scheduled interventions including surgery due to shortage of beds or personnel: according to a survey by the association of private insurance companies (*Verband der Privaten Krankenversicherungen*; PKV), 24 % of patients with chronic diseases moved their appointments and the *Deutsche Krankenhausinstitut* (German hospital institute; DKI) reported that 41 % of scheduled in-patient and 58 % of out-patient surgical interventions were postponed.

The RWTH Aachen University Medical Center was one of the first hospitals in Europe to care for COVID-19 patients due to a local coronavirus breakout in early spring of 2020 [4]. We sought to capture the impact of COVID-19 on patients with myeloproliferative neoplasms (MPN) in Germany in order to better understand and address their needs. Therefore, we developed the German Study Group for MPN (GSG-MPN) COVID patient survey within the GSG-MPN bioregistry. Since 2015, this non-interventional registry has enrolled more than 4000 patients with BCR-ABL1 negative MPN and now offers the possibility to implement patient surveys to defined situations such as the COVID pandemic.

The MPN−COVID-19-Survey was carried out between July and November 2020 in seven study centers of the GSG-MPN (hospitals and private practices), thereby covering the first wave and the beginning of the second wave of the COVID-19 pandemic. 15 questions regarding COVID-related symptoms, SARS−COV-2 test results, and MPN therapy were provided to the patients either as a paper-based or online survey (see Table 1). Only patients who had already given their consent to the GSG-MPN registry were included in the MPN−COVID-19-Survey. All patients agreed to data processing and data transfer. The survey was approved by local ethics committees. Additional data were taken from the GSG-MPN bioregistry database.

271 patients completed the questionnaire. Interestingly, no MPN patient reported a COVID-19 infection or a positive SARS−COV-2 test result during the survey period. This was unexpected, given rates of 1.3 % and 3.57 %, respectively, in the German population according to data published by the *Robert Koch Institute* [5]. These data suggest that the MPN patients participating in this survey were more successful in preventing a SARS−COV-2 infection than the general population. Even the patients' relatives showed lower infection rates, as only 1 % (n = 4) of contact persons were tested positive for SARS−COV-2. 99 % of our patients used a medical mask ("mouth-nose protection") and 26 % had undergone optional self-quarantine.

Asked about changes in medical care, our patients described that 30 % of visits in outpatient care (routine MPN checkups) had been rescheduled. Of these visits, 39 % have been rescheduled by the physician and 47 % by the patient (13 % indicated that their visits had been rescheduled but gave no further information). Among the patients with postponed appointments, only 30 % had a consultation by phone instead.

In a second part of our survey, patients were asked if they had faced any problems in receiving their therapy during the lockdown/pandemic. Of the 270 patients answering the question about the MPN therapy, 178 (66 %) received MPN-specific treatment during the time interval, while 92 (34 %) underwent watchful waiting. Of the 178 patients, 52 patients received hydroxyurea (HU) (29 %), 26 interferon (15 %), 62 a JAK inhibitor (35 %), 14 anagrelide (8 %) and 4 (2 %) of the patients received other MPN treatments such as medication within a clinical trial, allogenic stem cell transplantation, or imatinib (in two cases of MPN with a Pdgfra-, Pdgfrb- or Fgfr aberration). 20 patients (11 %) received more than one medication (e.g. HU or imids plus JAK inhibitor). 98 % of the 178 patients had no changes in their medication. Only 4 (2 %) patients experienced changes of their MPN-treatment due to the pandemic (1 dose reduction of interferon, 1 dose increase of JAK inhibitor, 2 changes in medication from anagrelide to JAK inhibitor and from HU plus anagrelide to interferon).

Only 10 (6 %) out of 160 patients answering the question whether they had experienced challenges to receive their medication, reported problems: this included problems with the pharmacy (4 %), problems to obtain a prescription (1 %), or further unspecified problems (1 %).

Patients with hematological malignancies seem to have an increased risk of a severe COVID-19 course and an increased need for hospitalization and intensive care compared to patients with other cancers [6]. Furthermore, Passamonti et al. described an increased mortality rate of symptomatic COVID-19 patients with hematological malignancies, 41 times higher compared to a non−COVID-19−Cohort with hematological malignancies and 4 times higher than in the general population with COVID-19 (without hematological malignancies), but the MPN disease itself was not predictive for a poor COVID-19 infection outcome [7]. Conversely, an European analysis demonstrated that mortality in MPN

https://doi.org/10.1016/j.leukres.2021.106646
Received 2 April 2021
Available online 16 June 2021

Table 1
Results of the GSG-MPN−COVID-survey.

Demographics										
Age at MPN diagnosis, years - median (range), n = 271			Age at completing survey - median (range), n = 271		Male/female, n = 271			MPN subtype, n = 255		
51 (17−84)			59 (18−90)		118 (44)/ 153 (56)			PV	ET	MF	Other MPN
								73 (29)	99 (39)	72 (28)	11 (4)
Symptoms since march 2020										COVID test	
Coughing, n = 270		Fever, n = 271	Loss of sense of smell and taste, n = 271	Rhinitis, n = 271		Scratchy throat, n = 271		Shortness of breath, n = 270		Tested for COVID-19 (n = 270)/ positive results	
33 (12)		10 (4)	13 (5)	31 (11)		39 (14)		18 (7)		43 (16)/ 0 (0)	
Outpatient treatment, n = 251											
No rescheduled appointments, n = 251			Rescheduled appointments, n = 251		Rescheduled by physician, n = 76		Rescheduled by patient, n = 76		Consultation via phone, n = 76		
175 (70)			76 (30)		30 (39)		36 (47)		23 (30)		
MPN-treatment, n = 270		MPN therapy, n = 178						Problems to recieve MPN medication, n = 160			
No	Yes	HU	IFN	JAK-inhibitor	Anagrelide	Combination	other	Yes	Delivery issues in pharmacy	Issues to get a prescription	Problems with intake of medication
92 (34)	178 (66)	52 (29)	26 (15)	62 (35)	14 (8)	20 (11)	4 (2)	10 (6)	7 (4)	1 (1)	0 (0)
Changes in MPN-medication n = 178								Vaccination			
No changes		Dose reduction	Dose increase	Change to other drug		Discontinuation		Influenza, n = 270		Pneumococcus, n = 253	
174 (98)		1 (1)	1 (1)	2 (1)		0 (0)		162 (60)		91 (36)	
Previous/ concomitant diseases, n = 253											
Heart diseases (e.g. myocardial infarction, cardiac insufficiency)			Arterial hypertension	Autoimmune diseases	Lung diseases	Thrombolic/embolic events		Severe bleeing events	Malignant diseases	Diabetes	(Ex) smoker
30 (12)			84 (33)	26 (10)	16 (6)	72 (28)		13 (5)	19 (8)	20 (8)	35 (14)

*Other MPN = Chronic neutrophilic leukemia, MPN unclassified myeloid neoplasm with eosinophilia, and rearrangement of FDGFRA, FDGFRB or FGFR1.
PV Polycythemia vera, ET Essential thrombocythemia, MF Myelofibrosis (incl. Sec. MF from ET/ PV).

patients with COVID-19 was higher than in the general population and highest in MF patients [8].

The German guidelines on treatment during COVID-19 pandemic recommend to make decisions on cancer treatment on an individual basis but to keep in mind, that a well-controlled therapy can affect infection courses positively [9]. In MPN patients, severe withdrawal syndromes, especially after ruxolitinib cessation, may occur [10,11] and have been described to possibly worsen the COVID-19 course [8]. Therefore, currently, there is a general agreement (e.g. in the guidelines of the EHA infectious disease Scientific Working group [12]) to continue therapy in MPN patients. According to our survey, the acceptance of these recommendations is quite high.

In case of a SARS−COV-2 infection in MPN patients, the decision on how to proceed with the ongoing medication becomes more complicated. Recent trials suggested that Janus-activated kinase (JAK) inhibitors such as ruxolitinib might treat SARS-CoV-2 induced systemic hyperinflammation [13] as the JAK/STAT pathway is linked to inflammatory processes [14]. However, in the RUXCOVID trial (NCT 043,621, 379), a phase III multicenter, randomized, double-blind, placebo-controlled 29-day study to evaluate the efficacy and safety of ruxolitinib plus standard of care (SoC) therapy compared to placebo plus SoC therapy in patients aged ≥12 years hospitalized for COVID-19 and not intubated or receiving ICU care prior to randomization, which enrolled 432 patients globally, the primary endpoint was not met (proportion of patients who died, or required mechanical ventilation due to respiratory failure or ICU care by Day 29) [15]. And it remains unclear if ruxolitinib or other immunosuppressive drugs increase the risk of developing COVID-19. MPN patients are at high risk of thromboembolic events [16]. Thrombembolic events have been described as one of the major complications during SARS−COV-2 infection leading to a worse outcome [17,18]. In a recent analysis by Barbui et al., the essential thrombocythemia MPN subtype was associated with the greatest risk of venous thromboembolism during COVID-19 [19].

Since none of our patients was affected by COVID-19, questions concerning their outcome remain to be answered in the next parts of this ongoing survey.

In summary, our patients successfully prevented infections with SARS−COV-2, but they did face challenges in their regular follow-up or, sometimes, in receiving their medication. The use of video-based teleconsultation or contact-free ways of getting a medical prescription may be a means to overcome these challenges. In contrast to countries with the geographical need to implement such methods in daily routine (such as Australia or India), the use of teleconsultation in Western Europe is still focused on specialized fields such as emergency medicine/stroke/myocardial infarction. As reported in a national online survey [20], telemedicine was routinely used by only 19.6 % of the medical staff in different health care settings in Germany (private practices or hospitals and university hospitals) [20]. Thus, better use of telemedicine may improve the care of MPN patients during the present and potential upcoming pandemics.

Author contributions

K. Kricheldorf and S. Isfort designed the study, collected data, analyzed the data, discussed the data, and wrote the manuscript. S. Koschmieder designed the study, collected data, discussed data, analyzed data and edited the manuscript. F. Stegelmann, R. Hansen, F. Lang, T.H. Brümmendorf, K. Döhner, P. Jost, M. Radsack and V. Heuer collected data and edited the manuscript. All authors approved the final version of the manuscript.

Declaration of Competing Interest

KK reports no conflict of interest.

KD reports advisory board activity for Novartis, BMS/Celgene CTI Biopharma; honoraria and research funding from Novartis and BMS/Celgene.

FS reports speaker bureau and consultancy for BMS, Incyte, Novartis, and Pfizer.

P.J.J. has had a consulting or advisory role, received honoraria, research funding, and/or travel/accommodation expenses from: Abbvie, Bayer, Boehringer, Novartis, Pfizer, Servier, Roche, BMS and Celgene

FL receives support from the Frankfurter Förderung “Nachwuchswissenschaftler” and the EUTOS funding program. FL had advisory roles for Novartis, Ariad, Sanofi Aventis and Bristol-Myers Squibb. FL received funding of Novartis.

MR reports advisory board activity for Novartis, BMS,Celgene, Incyte, Otsuka, Daiichi Sankyo, AOP Pharma, Takeda; honoraria from Novartis, Takeda, Celgene, BMS; and other financial disclosures (i. e. travel support) from Abbvie, Astellas, Daiichi Sankyo, Celgene, JAZZ Pharma.

RH reports no conflict of interest.

VH reports no conflict of interest.

RR reports no conflict of interest.

THB reports advisory board activity for Pfizer, Novartis, Merck and Janssen; honoraria from Novartis, and Pfizer; research funding from Novartis and Pfizer.

SK reports advisory board activity for Pfizer, Incyte, Ariad, Novartis, AOP Pharma, BMS, Celgene, CTI, Roche, Baxalta, Sanofi, Geron, and Janssen; honoraria from Novartis, BMS, Celgene, Pfizer, Incyte, Ariad, Shire, Roche, AOP Pharma, Geron and Janssen; research funding from Novartis Foundation, BMS, Novartis, and Janssen; and other financial disclosures (i.e. travel support) from Alexion, Novartis, BMS, Celgene, Incyte, Ariad, AOP Pharma, Baxalta, CTI, Pfizer, Sanofi, Shire, Geron and Janssen.

SI reports board activity for Pfizer, Ariad and Novartis; honoraria from Ariad, BMS, Incyte, Novartis and Pfizer; and other financial disclosures (i.e. travel support) from Alexion, Amgen, Hexal, Mundipharma, Novartis, Pfizer and Roche.

Acknowledgements

KK was supported by the Task force COVID-19 Forschungsnetzwerk of the Faculty of Medicine of RWTH Aachen University. This work was in part supported by the Stiftung Universitätsmedizin of the RWTH Aachen University to KK, TB, and SK for the maintenance of the bioregistry. We thank Britta Wagner for secretarial assistance and Benedikt Bender for programming the survey. We thank the members of the German Study Group for MPN (GSG-MPN), the mpn netzwerk e.V. patient advocacy group, and our patients for supporting this survey and the GSG-MPN bioregistry.

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