



Impact of SARS-CoV-2 pandemic on rehabilitation of patients after high-dose chemotherapy with allogeneic hematopoietic stem cell transplantation: results of a monocentric, retrospective analysis

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Abstract

Objective Because immunocompromised patients are particularly vulnerable during the SARS-CoV-2 pandemic, patients undergoing high-dose chemotherapy with allogeneic hematopoietic stem cell transplantation (HDC/alloSCT) face the question of whether they should enter a rehabilitation stay. We therefore asked to what extent the pandemic has changed the acceptance of a rehabilitation stay and whether and how high the risk of infection for these patients should be assessed.

Methods We analyzed all patients after HDC/alloSCT admitted to our rehabilitation facility during the period, since the first SARS-CoV-2 wave occurred in Germany (03/15/2020) and compared them with patients admitted to our rehabilitation facility before.

Results Analysis of our data showed a significant reduction in rehabilitation stays of patients after HDC/alloSCT during the SARS-CoV-2 pandemic. Patients arrived for rehabilitation significantly later after HDC/alloSCT and were less likely to take immunosuppressive medications. The anxiety score in the HADS was lower and the platelet count was higher. In contrast, parameters such as age, sex, or leukocyte value did not play a role. None of the patients became infected with SARS-CoV-2 during rehabilitation.

Conclusions The acceptance of a rehabilitation stay during the SARS-CoV-2 pandemic has changed, but there does not seem to be an increased risk for the patients.

Keywords Rehabilitation · SARS-CoV-2 pandemic · Allogeneic · Stem cell transplantation · Immunosuppression

Introduction

Medical rehabilitation differs considerably from one European country to another. In most countries, rehabilitation is predominantly carried out on an outpatient basis. In

Germany, it is predominantly carried out on an inpatient basis as a compact 3-week service and is an integral part of the healthcare system. After completing the oncological treatment, every patient has the right to an outpatient or inpatient rehabilitation. Its overall goals are to restore or improve health to avoid long-term care or disability, and to preserve patients' earning capacity.

In 2020, we could show that a rehabilitation stay for patients with hemato-oncological diseases carries an increased risk of being transferred to an acute clinic during the rehabilitation stay due to complications compared to patients with solid tumors. Thus, the most common reason for early termination of a rehabilitation stay was CMV reactivation or fever (Kiefer et al. 2020). This is especially true for patients after high-dose chemotherapy with allogeneic hematopoietic stem cell transplantation (HDC/alloSCT), who must be assumed to have a particularly weakened immune system (Lum 1987; Park et al. 2015; Mehta and Rezvani 2016). However, we were also able to show that

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the reasons for premature discontinuation of the rehabilitation stay are not related to the rehabilitation, but are due to therapy- or disease-related immunosuppression (Kiefer et al. 2020).

In 2020, the global SARS-CoV-2 pandemic also reached Germany and continues to this day with varying intensity. SARS-CoV-2 is primarily transmitted from person to person, and immunosuppressed patients are at particular risk from SARS-CoV-2 infection (Ljungman et al. 2021; Sharma et al. 2021). Since a rehabilitation stay is of proven benefit for patients after HDC/alloSCT (Bertz 2021; Abo et al. 2021) and every patient in Germany is entitled to rehabilitation, the question arises whether a rehabilitation stay during the SARS-CoV-2 pandemic can be recommended for patients after HDC/alloSCT. In this work, we address the question of how to assess the risk for patients after allogeneic hematopoietic stem cell transplantation in times of the SARS-CoV-2 pandemic. Are the patients with particular immunodeficiency at increased risk of contracting SARS-CoV-2 infection during a rehabilitation stay and what hygienic precautions may be useful to minimize the risk for these patients to contract SARS-CoV-2?

Methods

The rehabilitation facility in which the following analyses were carried out rehabilitates patients with oncological, gastroenterological or cardiac diseases and is located near Berlin, the capital of Germany. About 40% of the patients treated in the oncology department are breast cancer patients, 40% of patients with gastrointestinal cancers, and 20% are hemato-oncological patients. The training intensity is adjusted to the heart rate, so that too much stress is avoided. Patients with platelets below 50×10^9 (GPT)/L perform a moderate and low-vibration training. All patients are

kept in single rooms, except for those who are rehabilitating with their partner and prefer a double room. The rooms are comparable to a hotel room (own bathroom, carpet, curtains, telephone, television, Internet access, etc.). The philosophy of rehabilitation is to avoid as much as possible anything that reminds the patient of the previous hospital stay.

Study population

We analyzed all patients after HDC/alloSCT, who had been rehabilitated in our rehabilitation facility over the period between 01 Jan 2019 and 30 June 2022 and compared patients admitted to our rehabilitation facility before the first SARS-CoV-2 wave that occurred in Germany (15 March 2020) with those admitted after. The data were collected within a monocentric, retrospective analysis and were taken from the medical records. There was an average of 236 days (median) between stem cell transplantation, and the start of the rehabilitation stay, which lasted 20 days (median, range 2–30). For more information on patient characteristics, see Table 1. An ethical approval for this study was not required, because the collection of data was from the medical reports, which were part of the standard care program. All information was kept confidential.

Special hygienic conditions

The rehabilitation of patients with hemato-oncologic diseases after HDC/alloSCT is carried out under special hygienic conditions considering the weakened immune system of the patients. The aim is to minimize contact with potentially infectious rehabilitants as much as possible and thus reduces the risk of infection for hemato-oncological patients. The special hygienic conditions for patients after HDC/alloSCT, which were common in our rehabilitation facility before the SARS-CoV-2 pandemic, are described

Table 1 Patient characteristics

Number of rehabilitation stays	75
Age (median)	58.5
Women/men (%)	38/37 (50.7/49.3)
Time between HDC/alloSCT and start of rehabilitation stay (days; median, range)	236 (48–1154)
Number of patients with immunosuppression during the rehabilitation stay (%)	38 (50.79)
Diseases	
Acute myelogenous/lymphatic leukemia (de novo and secondary)	42
Myelodysplastic syndrome	12
Non-Hodgkin lymphoma (B and T cells)	10
Myeloproliferative disorders	8
Hodgkin disease (relapse)	1
Aplastic anemia	1
Wiskott–Aldrich syndrome	1

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in our previous publication (Kiefer et al. 2020). In brief, patients' rooms were cleaned 6 times per week, disinfection of all disinfected surfaces was carried out six times per week, and bed linen was changed three times per week. All patients were repeatedly motivated to disinfect their hands. Patients took their meals in separate room to which other patients have no access. Therapies were carried out during the rehabilitation stay in individual therapy or in very small groups (up to three patients). All therapists are regularly trained in adequate hygiene in contact with immunocompromised patients. They are also taught how to recognize the typical signs of graft-versus-host disease (GvHD) and infection. To detect complications at an early stage and to be able to react to them in time, patients are visited five times a week and a physician experienced in the treatment of immunosuppressed patients is always on call.

During the course of the SARS-CoV-2 pandemic, new hygiene rules have been added to those already in place. With the availability of sufficient FFP2 masks, all patients and all employees of the rehabilitation facility were required to wear them properly. In addition, patients were no longer allowed to receive visitors during their rehabilitation stay. From the availability of the rapid antigen test-based for SARS-CoV-2 detection, all patients were tested at the beginning of the rehabilitation stay and again the day after next or if patients reported symptoms that may be related to SARS-CoV-2 infection (e.g., fever, rhinitis, difficulty swallowing, headache, and impaired sense of taste or smell). In the two episodes of an SARS-CoV-2 outbreak in our rehabilitation facility, all patients were even tested daily. A positive test resulted in immediate isolation of the patient and discharge home if medically justifiable. Otherwise, the patient was transferred to an acute hospital.

Influence of SARS-CoV-2 infections on rehabilitation

To analyze to what extent the SARS-CoV-2 pandemic has changed the willingness of patients after HDC/alloSCT to

take advantage of a rehabilitation stay, we compared the frequency of rehabilitation stay in patients after HDC/alloSCT during the SARS-CoV-2 pandemic with the pre-pandemic period. Additionally, we examined whether patients during the SARS-CoV-2 pandemic differed from those before the pandemic. For this purpose, we compared the age of the patients at the beginning of the rehabilitation stay, their current immunosuppression, and other parameters.

From the medical reports, we recorded all oncology patients in whom SARS-CoV-2 infection was detected (nasopharyngeal RT-PCR in a certified laboratory) during the rehabilitation stay.

In analyzing these data, we compared the frequency of SARS-CoV-2 infection in patients after HDC/alloSCT with those who had not received such therapy, but were undergoing rehabilitation for oncologic disease.

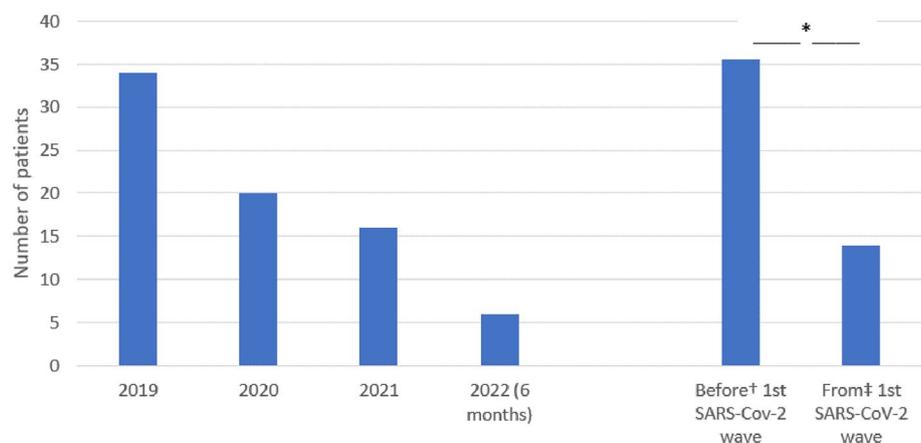
Statistical methods

Statistical analyses were performed using WinSTAT (WinSTAT for Microsoft Excel, Version 2012.1, R. Fitch Software). Differences between groups of patients were analyzed using t test for continuous variables and Chi-squared tests for categorical variables. *p* Values < 0.05 were considered statistically significant.

Results

The frequency of patients who completed a rehabilitation stay in the years from 1 January 2019 to 30 June 2022 falls steadily as the pandemic progresses (Fig. 1). A comparison of the time before the first SARS-CoV-2 wave (1 January 2019 to 14 March 2020; 14.5 months) with the time from the first SARS-CoV-2 wave (15 March 2020 to 30 June 2022; 27.5 months) shows that the willingness to have a rehabilitation stay during times of the pandemic decreases

Fig. 1 Number of patients with rehabilitation stay after HDC/alloSCT, †between 01 Jan 2019 and 14 March 2020 calculated on 12 months, ‡between 15 March 2020 and 30 June 2022 calculated on 12 months, **p* < 0.05. Graphic done by Excel, Windows



significantly. A frequency of rehabilitation stays calculated on 12 months is shown in Fig. 1 (35.5 patients/year before the first wave of the pandemic, 13.9 patients/year from the first SARS-CoV-2 wave, $p < 0.05$).

Furthermore, we wondered whether the patients who came for rehabilitation during the pandemic differed from those before the pandemic (Table 2). Patients after HDC/alloSCT who completed the rehabilitation stay during the SARS-CoV-2 pandemic showed less frequent drug immunosuppression ($p < 0.01$), greater temporal distance between allogeneic transplantation and the start of the rehabilitation stay ($p < 0.05$), a lower Hospital Anxiety and Depression Scale (HADS) anxiety score ($p < 0.05$), and a higher platelet count ($p < 0.01$).

No differences ($p > 0.05$) were observed for age, sex, leukocyte count, absolute neutrophil count, hemoglobin level, renal function, C-reactive protein (CRP), medication with antiviral, antibiotic, or antifungal, body mass index (BMI), HADS depression score, or whether the patient had ever suffered from graft-versus-host disease (GvHD).

We were also interested in how many of the patients after HDC/alloSCT became infected with SARS-CoV-2 during their rehabilitation stay. Fortunately, in the period from the first SARS-CoV-2 wave (15 March 2020) to the end of data collection (30 June 2022), none of the 32 patients who underwent a rehabilitation stay in our hospital after HDC/alloSCT became infected with SARS-CoV-2. In contrast, of the remaining oncology patients who had not been treated with HDC/alloSCT (especially breast and digestive tract tumors; $n = 2147$), 13 patients became infected during the same period.

Discussion

Main findings

The immune system of patients with hemato-oncological diseases is weakened, and therefore, these patients are at increased risk of acquiring life-threatening infections. This is especially true for patients after HDC/alloSCT. Therefore, even before the global SARS-CoV-2 pandemic, these patients were advised to avoid crowds and to critically consider participation in a rehabilitation stay. In the beginning of 2020, we were able to show that under tightened hygiene conditions, a rehabilitation stay posed no additional risk to patients with hemato-oncologic diseases (Kiefer et al. 2020). Among the patients analyzed at that time were 35 patients after HDC/alloSCT.

The analysis of our current data aims to investigate the impact of the SARS-CoV-2 pandemic on the rehabilitation of patients after HDC/alloSCT. Because these patients are particularly vulnerable to SARS-CoV-2, we focused our analyses exclusively on this group of patients. First, we asked to what extent the pandemic affected the rehabilitation of patients after HDC/alloSCT. Our data clearly show that significantly fewer patients after HDC/alloSCT had a rehabilitation stay in our clinic during the pandemic period. Perhaps, this is because fewer patients overall were treated with HDC/alloSCT during the SARS-CoV-2 pandemic (Passweg et al. 2022). It is also possible that the reason for this was either patient caution, the recommendation of the attending physician, or both. There were no restrictions on the part of our clinic regarding rehabilitation of these patients. Comparing patients who underwent a rehabilitation stay in our clinic before with those who underwent a rehabilitation stay after SARS-CoV-2, it is

Table 2 Differences in patients before and during the SARS-CoV-2 pandemic

	Before [†] SARS-CoV-2 pandemic	After [‡] SARS-CoV-2 pandemic	Significance
Number of patients	43	32	$p < 0.05$
Patients with immunosuppressive medication	28	10	$p < 0.01$
Temporal distance between allogeneic transplantation and the start of the rehabilitation stay (days, median)	159	311	$p < 0.05$
HADS anxiety score (median)	6.72	4.78	$p < 0.05$
Platelet count (median)	147	213	$p < 0.01$
Age, sex, leukocyte count, absolute neutrophil count, hemoglobin level, renal function, C-reactive protein, medication with antiviral, antibiotic, or antifungal, body mass index, HADS depression score, ever suffered from graft-versus-host disease			n.s

n.s. not significance, HADS hospital anxiety and depression scale

[†]Between 01 Jan 2019 and 14 March 2020

[‡]Between 15 March 2020 and 30 June 2022

noticeable that patients during the pandemic took longer to start a rehabilitation stay. The longer ago the allogeneic SCT, the more often immunosuppressive drugs could be discontinued, and the better the immune system recovered. It can be assumed that patients countered their fear of SARS-CoV-2 infection during the rehabilitation stay by waiting for their immune system to improve. It is also reflected in the anxiety score (HADS) that patients started a rehabilitation stay during the pandemic only if they had less anxiety.

It is noticeable that parameters that are easy to assess, such as time since allogeneic SCT and immunosuppressive medication, are more decisive than parameters that are more difficult to interpret (leukocyte count, absolute neutrophil count, hemoglobin level, renal function, C-reactive protein, whether the patient had ever suffered from graft-versus-host disease, medication with antiviral, antibiotic, or antifungal). This may indicate that the decision whether and when to seek rehabilitation was made by the patient rather than by the treating physician.

Platelet levels were also statistically significantly higher in patients during the pandemic. This is interesting, because we had already found a low platelet value as a negative prognostic parameter for a complication during the rehabilitation stay in our publication (Kiefer et al. 2020).

Considering that elderly patients are particularly at risk from SARS-CoV-2 (Chen et al. 2020; Docherty et al. 2020; Wang et al. 2020), even when vaccinated (Blomberg and Frasca 2011; Lo Sasso et al. 2021; Müller et al. 2021), it is interesting to note that age did not influence the decision to stay or not stay in rehabilitation.

Also of particular interest was the extent to which patients are at risk of SARS-CoV-2 infection after HDC/alloSCT. Analysis of all the patients without HDC/alloSCT who underwent rehabilitation during the pandemic revealed that 13 patients of the 2147 patients became infected with SARS-CoV-2. Fortunately, none of the 35 patients after HDC/alloSCT became infected during the SARS-CoV-2 pandemic. Several reasons could be responsible for this. It could be advantageous that a special hygiene regime is applied to patients undergoing a rehabilitation stay in our hospital after HDC/alloSCT. We suspect that most patients become infected during their rehabilitation stay while eating together in a dining hall. This is the only moment when they put down the FFP2 masks and often have a conversation with their tablemates. We believe, in particular, the fact that these patients take their meals in a separate room to which other patients do not have access significantly reduced the risk of infection. The fact that patients undergoing HDC/alloSCT are trained to follow correct hygienic guidelines (Brandt and Broadbent 1994; Hayes-Lattin et al. 2005) due to significant immunosuppression may also have contributed.

Comparison with previous literature

To our knowledge, such an analysis on the impact of the COVID-19 pandemic on rehabilitation of patients after HDC/alloSCT has not been done before. Our 2020 analysis (Kiefer et al. 2020) on the risk of a rehabilitation stay for immunocompromised patients had shown that with a strict hygiene regime, there is no increased risk for patients after HDC/alloSCT to suffer complications leading to a discontinuation of the rehabilitation stay. The positive effect of our hygiene regime, which we intensified during the pandemic, now seems to be confirmed for the SARS-CoV-2 pandemic.

Limitations and strength

Some limitations should be noted when interpreting the results of this study. These are monocentric results with only a limited number of patients. Further studies should therefore be multicenter and performed on a larger number of patients after HDC/alloSCT and in different countries. In addition, certain hygiene standards are maintained in our rehabilitation facility, which are only possible with a high commitment of the staff, but also with increased costs. As in our previous study, we cannot assess the extent to which these standards are necessary. Again, further studies would have to be initiated at hospitals with different hygiene concepts.

The strength of our study is that we have now been able to show for the first time that the rehabilitation stays that are so necessary for patients can also be performed without increased risk for the most vulnerable patients after allogeneic hematopoietic stem cell transplantation, even during the SARS-CoV-2 pandemic. The results of all patients of our rehabilitation facility during more than 2 years of SARS-CoV-2 pandemic show this clearly. It is also interesting to analyze the characteristics of our patients who underwent rehabilitation in our clinic during the SARS-CoV-2 pandemic. It shows according to which criteria patients are very likely to decide for or against rehabilitation. Whether these criteria are actually necessary, however, remains an open question.

Implications for practice and research

Our results show that a rehabilitation stay can be recommended to patients after HDC/alloSCT patients even in a SARS-CoV-2 pandemic. Suitable hygiene conditions neutralize a combination of a weakened immune system (as a result of HDC/alloSCT), the special situation of a rehabilitation facility and the SARS-CoV-2 pandemic, which does not stop at rehabilitation facility. As mentioned above, further studies should be carried out at other rehabilitation facility to verify these results and to test the success of other hygiene

regimes. However, one should always be aware that even the most well-designed hygiene regime only works in practice if the patients and all professional groups in the rehabilitation facility (i.e., doctors, nurses, cleaning staff, physiotherapists and sports therapists, kitchen staff, and the management of the clinic) conscientiously follow the guidelines implement.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by TK, CL, HV, and GD. The first draft of the manuscript was written by TK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval/consent to participate Since it is a retrospective analysis, no patient consent and ethics committee approval were done.

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