

CORRESPONDENCE



Defining the impact of SARS-COV-2 on delivery of CAR T-cell therapy in Europe: a retrospective survey from the CTIWP of the EBMT

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Bone Marrow Transplantation (2022) 57:299–301; <https://doi.org/10.1038/s41409-021-01483-8>

TO THE EDITOR:

Since its discovery in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/ COVID-19) pandemic has caused a documented 172.99 million confirmed cases and 3.72 million deaths [1]. This has had an unprecedented impact on the delivery of cancer therapy across the globe, warranting all health care providers to reassess their services and management protocols, with CAR T-cell therapy being no exception [2]. Given the complexity of delivery of CAR T-cell therapy for haematological malignancies, including products being manufactured on a per-patient basis; treatment centres also providing cell procurement services; the need for transportation of leucapheresate and CAR-engineered product to and from manufacturing sites often across national borders; requirement for fixed manufacturing intervals; requirement for in-patient and/or ICU beds, we sought to define the impact of the pandemic on delivery of CAR T-cell therapies in Europe.

On behalf of the Cellular Therapy and Immunobiology Working Party (CTIWP) of the EBMT, we carried out a snapshot survey of EBMT centres (Supplementary Appendices 1 and 2), to define the impact of the pandemic and associated socio-economic restrictions on academic and clinical CAR T-cell activity from January 2020 to the time that the questionnaire was completed (the survey was first posted July 13, 2020, and closed in Nov 2020). This reporting interval effectively captures the impact of the first wave of the pandemic in Europe. For the purposes of the survey, partial lockdown was defined as restrictions allowing local/regional travel, phased re-opening of shops/restaurants/services and the complete lockdown was defined as leaving home only to attend essential jobs, buy food/medicine or attend hospital. In this survey, it was not our intention to determine the patient-related impact of COVID-19 infection, as this is the subject of investigation of the EBMT COVID-19 taskforce.

In all, 49 out of 118 centres in 12 countries responded to the survey (listed in Supplementary Appendix 3), giving a response rate of 42%. 49% of responding centres deliver licensed CAR T-cell therapy for both B-ALL and B-NHL indications with a further 35% delivering these in association with CAR T-cell studies (Supplementary Table 1). The majority of centres (60%) were dealing with industry-sponsored studies whilst 33% were engaged in academic CAR T-cell studies. To assess CAR T therapy activity per centre as a baseline prior to the COVID-19 pandemic, centres reported the number of CAR T infusions delivered in 2019. The median number of CAR T-cell infusions carried out in these centres during 2019 was 8 (range 0–68), with the majority of centres (59%) carrying out 0–10 infusions.

At the time of completing the survey, 25/49 (51%) of centres were subject to partial lockdown restrictions, 4% were under complete lockdown and 45% were without any restrictions. New and total cases per million, as well as hospitalised case rates during the reporting, are shown (Supplementary Figs. 1 and 2). In total, 25/49 (51%) of centres reported a reduction in departmental capacity for patients as a result of the COVID-19 pandemic, and 24/49 (49%) of centres stated they did not. The most commonly cited causes for this reduction in capacity were patient factors (14/25, 56% e.g. too unwilling or unable to travel), reduction in in-patient beds (13/25, 52%), reduced ICU access (12/25, 48%), reduced clinical trial activity (12/25, 48%), proven or unproven COVID-19 infection (12/25, 48%) and reduced out-patient provision (11/25, 44%). For this analysis, multiple factors could be reported by each centre. Less frequent causes included delay in manufacture (6/25, 24%) or reduced access to tocilizumab (3/25, 12%).

In all, 14/49 (29%) of centres stated that CAR T-cell therapy was delayed for at least one patient. In total, 8/14 centres (57%) had 1–2 patients delayed; 5/14 centres (36%) had 3–5, and 1 centre (7%) had 7 patients delayed due to COVID-19. A histogram of the number of delayed patients in centres arranged by their pre-COVID-19 CAR T activity is shown in Fig. 1a. The expected number of CAR T patients treated during the pandemic by the time of survey reporting was calculated based on the pre-COVID-19 CAR T activity. From this, a normalised value for the delayed patients by expected 2020 centre activity was calculated (ratio of delayed to expected patients). This ratio is depicted alongside country-specific total COVID-19 cases at the time the centre returned the survey (Fig. 1b) as well as by new COVID-19 cases per million (Supplementary Fig. 3).

Of 31 completed questionnaires on delayed patients, the median age was 62 years (range 8–75), 19/31 (61%) had DLBCL, 8/31 (26%) had B-ALL and 4/31 (13%) had another indication (myeloma or Richter's transformation of CLL, Supplementary Fig. 4). In all, 13/31 (42%) were being considered for axicabtagene ciloleucel, 8/31 (26%) were considered for tisagenlecleucel and 10 (32%) for another product.

The most commonly cited reasons for delay included reduced ICU access, reduction in rostered haematology medical team, reduction in in-patient beds (22, 7 and 5 reports, respectively). 19/31 (61%) of patients were delayed post apheresis but pre-infusion. Patients were most commonly delayed up to 1 month (17/31, 55%) though longer delays of 1–3 months were noted (in 7/31, 23%) and 2/31 (6%) were delayed for 4–12 months. In all, 5/31 (16%) of patients were delayed indefinitely. In total, 25/31 (81%) of patients were subsequently infused and in 5/31 (16%) of cases, CAR therapy was cancelled. In 15/22 (68%) cases, the delay resulted in a need for additional therapy prior to CAR T-cell therapy and in 12/22 (55%) cases, was

Received: 13 July 2021 Revised: 15 September 2021 Accepted: 23 September 2021
Published online: 20 November 2021

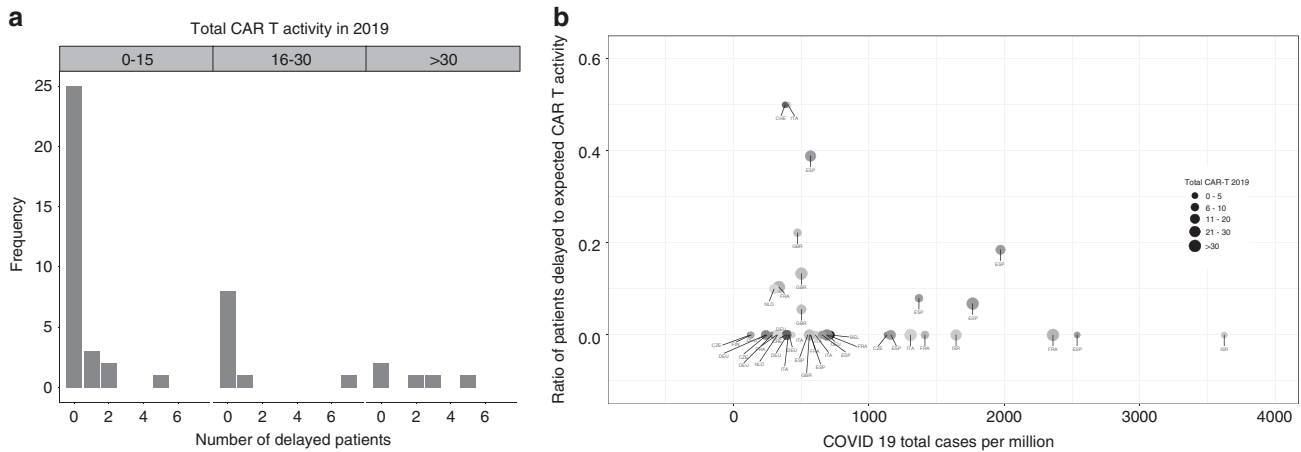


Fig. 1 Centres reported the absolute numbers of patients delayed in receiving CAR T-cell therapy during 2020 up to the point of survey submission. These data are depicted (a) stratified by the total CAR T activity for that centre in 2019 (pre-pandemic). The number of patients expected to have been treated in 2020 up to the point of survey submission was calculated based on reported CAR T activity in 2019. For each centre, a ratio of delayed to the expected number of treated patients was calculated. This is depicted (b), against the total country-specific cases of COVID-19 per million population at the point of survey reporting (data obtained from Our World in Data <https://ourworldindata.org/coronavirus#coronavirus-country-profiles>).

associated with disease progression (more than one outcome could be reported per patient, 22 patients with the reported impact of delay). Centres also provided details of complications associated with the delay in CAR T-cell therapy administration in nine cases. Death as a result of disease progression was documented in two cases, there were two cases of grade 4 cytokine release and there was one case of grade 3 ICANS.

CONCLUSIONS

The impact of the SARS-CoV-2/ COVID-19 pandemic on bone marrow registry activity and bone marrow transplantation have been reported [3] and guidelines implemented [2, 4–6]. A single US centre reported outcomes related to delay in the delivery of all cellular therapies including seven patients with delayed CAR T-cell therapy. However, the wider impact of the pandemic on access to and delivery of CAR T therapy has otherwise not been systematically documented.

We sought to define the impact of the pandemic on CAR T centres across Europe through the distribution of a snapshot survey with retrospective data collection capturing the first wave of the pandemic in 2020. In all, 51% of responding centres reported a decreased capacity for patients resulting from the pandemic. Just under a third reported a delay in delivery of CAR T therapy. The majority of centres with delayed patients reported 1–2 patients affected, mainly in the bridging period. Whilst most patients proceeded to infusion within one month of delay, there was a significant proportion (8/31, 26%) who experienced a delay of between 1 and 6 months and 5/31 (16%) who did not receive the therapy at all. Delay in CAR T-cell therapy was associated with a need for additional therapy as well as disease progression in 15/22 (68%). In 12/22 (55%) cases, the reporting clinician documented associated morbidity and mortality including death in two cases and severe CAR T-related toxicities, such as ICANS and CRS.

These data on the impact of restrictions related to the SARS-CoV-2/ COVID-19 pandemic on CAR T-cell therapy delivery are relevant to CAR T centres and health authorities for policy planning in response to successive pandemic waves and complement data from the biopharmaceutical industry highlighting the impact of the pandemic on cell and gene therapy discovery as well as delivery of licensed products [7]. Where possible, delays to CAR T-cell therapy delivery should be minimised to prevent adverse effects on patient outcomes, including the need for additional therapies and severe

CAR T-related toxicities known to be associated with a greater disease burden [8–11].

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AUTHOR CONTRIBUTIONS

SG, FM, MY, KM JH AR and CC designed the survey, reviewed the results, analysed results and wrote the manuscript. A U-I, JK, R de la C and PL contributed to the survey and study concept, reviewed the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41409-021-01483-8>.

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