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# Quantifying the available capacity and resource needs for provision of CAR-T therapies in the National Health Service in Spain: a survey-based study

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## ABSTRACT

**Objectives** To estimate the readiness of Spanish National Health Service (NHS) hospitals to provide chimeric antigen receptor T cell (CAR-T), and to identify and quantify the different resources needed to provide CAR-T considering three scenarios defined by 10, 25 and 50 patients per centre per year.

**Design** Targeted literature review and quantitative study using a questionnaire and telephone interviews. An algorithm was created to determine hospitals' readiness based on their capacity and capability. All the requirements for quantification were assessed and validated by the steering committee, formed by members of the Spanish Group of Haematopoietic Transplantation and Cell Therapy. A weighting system (from 0 to 1) was established for capability quantification. For resources quantification, a scoring system was established, with 0 points representing the minimum and 3 points the maximum of additional resources that a hospital indicated necessary.

**Setting** 40 Spanish hospital centres that perform allogeneic haematopoietic stem cell transplantation were invited to complete the questionnaire for capacity quantification, 28 of which provided valid responses. Nine hospitals participated in the interviews for resource quantification, eight of which had previously been designated by the Ministry of Health (MoH) to provide CAR-T.

**Outcome measure** Current capacity of NHS Spanish sites to administer CAR-T under different theoretical scenarios with varying numbers of procedures, and the potential healthcare resources that would be needed to realise the theoretical capacity requirements.

**Results** Four hospitals were optimally ready, 17 were somewhat ready and 7 were not ready. The actual extrapolated capacity of the currently designated MoH CAR-T sites would allow treatment of approximately 250 patients per year. Regarding healthcare resource needs, the numbers of haematologists, nurses and beds were the most important limiting factors, and those requiring further growth as patient numbers increased.

**Conclusions** Increasing the number of CAR-T-qualified centres and/or increasing resources in the current designated sites are two potential strategies that should be considered to treat CAR-T-eligible patients in Spain.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study presents an attempt to objectively quantify resources needed to implement and maintain a chimeric antigen receptor T cell (CAR-T) programme in the Spanish health system; the approach could potentially be used by other health systems with a similar structure.
⇒ Algorithms used in this study for the quantification of current capacity and resources, as well as the results obtained, have been validated by a steering committee of experts in the area of interest.
⇒ An objective combination of qualitative and quantitative criteria was used to assess National Health Service capacity.
⇒ The study identified which resources are the most limiting for the centres and which need to be increased when the number of CAR-T patients increases, which allows prioritisation for investment.
⇒ The main limitation of the study is the potential bias due to the potential for differences between participating and non-participating sites.

## INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma. Despite its clinically aggressive behaviour, it is potentially curable. However, approximately 40% of patients, after first-line treatment with immunochemotherapy combinations, will have refractory or relapsing disease.[1 2] In these cases, treatment consists of platinum-based salvage chemotherapy followed by autologous haematopoietic stem cell transplantation (auto-HSCT). Approximately 40–60% of patients with relapse or refractory disease respond to this chemotherapy treatment and 50% of them proceed

to an auto-HSCT, of which 30–40% remain progression free 3 years after transplantation.[2] However, patients who are not candidates for auto-HSCT because of age, comorbidities or lack of response to salvage chemotherapy, and those who relapse after transplantation, have an extremely poor prognosis. The results of a retrospective study show that the median overall survival in patients with primary refractory or a relapse less than 12 months after transplantation is approximately 6 months,[2 3] which highlights the need for new therapeutic options for these patients.[2]

In the case of precursor B cell acute lymphocytic leukaemia (B-ALL), the treatment goal in young patients is cure, which is achieved in a high percentage of children and young adults with standard chemotherapy regimens.[4–6] However, approximately 15–20% of patients will relapse.[7] In these cases, the treatment consists of salvage chemotherapy followed by allogeneic haematopoietic cell transplantation (allo-HCT), which is the only potentially curative treatment, but with a 5-year overall survival rate of 20–45% in this subgroup of patients.[7 8] In case of relapse after allo-HCT or in patients who are not candidates for allo-HCT (due to age, comorbidities, lack of donor, refractoriness of the ALL), there is no standard treatment other than clofarabine, which has shown poor results.[7]

Development and introduction of chimeric antigen receptor T cell (CAR-T) therapies (tisagenlecleucel and axicabtagen ciloleucel) have changed this scenario significantly, as this treatment has demonstrated in clinical trials a high response rate and duration of response in heavily pretreated adult patients with relapsed or refractory DLBCL and in high-risk paediatric and young adult patients with relapsed or refractory B-ALL.[2 9]

One of the main problems associated with the use of this therapy is its potential toxicity, which could require management of immunological events with biological drugs and heavy hospital support, including intensive care unit (ICU) admission in about 30% of patients.[10] This may require an intensive use of resources and accredited centres with multidisciplinary teams properly trained in the management of these complications.[3]

In addition, these innovative therapies imply a high economic and health impact, and also will compete for resources with other complex treatments such as haematopoietic transplantation. For these reasons and with the aim of organising the use of CAR-T therapies in an equitable, safe and efficient way, the Spanish Ministry of Health (MoH) developed a plan for their approach.[11]

This plan includes the designation of specific centres and pharmacoclinical protocols, aiming to establish criteria for the selection of patients and to monitor and evaluate the results to determine the therapeutic value of these therapies in real clinical practice. To this end, the responsible physicians have to register a series of data on patients who are being treated with CAR-T therapies in VALTERMED information system, a register established by the MoH to evaluate the efficacy and efficiency of drugs with high social or economic impact.

Moreover, among the criteria established for centres to be designated as authorised for the use of these therapies is that they should have JACIE-CAT-ONT (Joint Accreditation Committee of the ISCT and European Group for Blood and Marrow Transplantation, Transfusion and Cell Therapy Accreditation Committee, National Transplant Organisation) joint accreditation, to ensure that the centres have internationally accepted quality standards. The main criterion of this accreditation is to promote quality medical and laboratory practice in haematopoietic progenitor cell transplantation and related therapies using haematopoietic-derived cellular products.[12]

In Spain, there are currently 20 centres designated by the MoH for the administration of these therapies in adult patients and 10 for paediatric patients. In addition, four additional care centres have been designated in the event that the activity exceeds the designated qualified centres and one additional centre with exceptional nature.[11] Non-designated sites can apply for CAR-T treatment for a patient. The application is assessed first by a regional committee and then by a national committee. Once the treatment is approved, the patient is referred to a designated centre where apheresis, infusion and at least 1–3 months of follow-up after infusion are conducted.

The follow-up report on this plan, published in 2021, shows that in the 25-month period analysed from the first request (from 8 March 2019–31 March 2022), 768 requests have been received from 17 Autonomous Communities (AACC) and 139 hospitals.[13] Comparing these data with those of the previous year (May 2020), when a total of 271 applications were received, a continued increase in applications can be observed.[14]

Furthermore, in Europe, the European Medicines Agency (EMA) issued a positive opinion on the use of the European Society for Blood and Marrow Transplantation (EBMT) registry to capture long-term follow-up data of patients treated with CAR-T in European Union (EU) member states, with the latest report from March 2022 showing that the use of these therapies has increased in EU countries, with more than 3000 patients already registered.[15]

As previously discussed, it is necessary to use complex registries that are being consolidated (VALTERMED and the EBMT registry) but depend on the centres' resources. In addition, there is a commitment with the EMA to provide long-term information on the results, since they have conditional authorisations for the return of information.[15] Healthcare professionals need to dedicate time to fulfil all these reporting requirements to different partners, which has an impact from human resources' perspective.

Considering the reasons given above, it should be noted that introducing these therapies will require resources, planning and investment. This is why this study aims to quantify the healthcare resources necessary to be able to implement and provide treatment with CAR-T therapies, with the currently approved indications and future

indications that will be available in the near future, from the perspective of the Spanish National Health Service.

## METHODS

### Design

The study has been conducted, in collaboration with the GETH-TC (Spanish Group of Haematopoietic Transplantation and Cell Therapy), with the aim of obtaining a first approach to:

1. Quantify the current capacity of Spanish centres to administer commercial and/or academic CAR-T therapies in order to estimate whether the centres are more or less ready to provide this treatment. This will allow estimating whether it will be necessary to increase the number of qualified centres by the MoH to administer these therapies according to the estimated demand.
2. Identify and quantify the different requirements/resources at hospital level to provide CAR-T therapies considering different scenarios driven by the final number of patients per qualified site (10, 25 and 50 patients) in order to determine whether it would be necessary to increase the capacity of the current qualified sites in Spain or add additional resources to these sites.

All the requirements needed to quantify the current capacity of the sites were assessed and validated by a steering committee (SC) formed by Dr David Valcárcel, Dr Carlos Solano, Dr Pere Barba and Dr Pedro Castro designated by the GETH-TC to ensure maximum accuracy on the quantification process. SC members should fulfil the following two requirements: (1) haematology, ICU responsible or members from Spanish hospitals authorised to administer CAR-T therapies in 2019; and (2) members from GETH-TC. Criteria for assessment and interview questionnaire were developed based on findings of the targeted literature review and experience from the SC of the study. The questionnaires were pretested with members of the SC, who have similar experience as the candidates to complete the interviews.

First, in order to quantify the current capacity of Spanish centres to administer CAR-T, the 40 Spanish hospitals from 14 AACC with experience and capacity to perform allogeneic transplantation were selected, in a single-stage process, to complete an online cross-sectional questionnaire to collect the data required in relation to the resources needed. These sites were contacted via email and invited to participate. They were provided with a link, user and password to prevent multiple participation.

The questionnaire for the assessment included 63 qualitative and quantitative questions about: (1) total hospital capacity (availability of beds in transplant and haematology units, ICU beds and apheresis machines); (2) total current occupation at transplant and haematology units, ICU and apheresis unit (considering the number of patients admitted, the average days of hospitalisation and the apheresis length); (3) questions regarding human resources (availability of a case manager and/or administrative, social support, a CAR-T clinical team and the nurse/patient ratio). In addition, the centres were asked general questions regarding whether they had JACIE accreditation or experience in the use of CAR-T therapies, which are two of the criteria established by the MoH for the designation of centres to use these therapies (online supplemental table 1). Fieldwork was initiated on 7 October 2019 and closed on 6 February 2020. Biweekly reminders to promote participation and to complete the whole questionnaire were sent to the target centre representatives while the online survey was open.

Questions could be of different formats, such as long-answer text-type questions, short-answer text-type questions, yes/no questions, numerical answer questions, X-mark questions or multiple-choice questions. Then, an algorithm was created based on the capacity and capability of the centres to administer CAR-T therapies and was validated by the SC. In this algorithm, capacity and capability were defined by different resources with different weights. Using this algorithm and considering the responses of the different centres to the questionnaire, the hospital readiness of each centre to administer these therapies was estimated.

Only centres with a questionnaire completeness rate of more than 50% were considered on the final study sample and had their results analysed (online supplemental figure 1).

For the second assessment to quantify the resources needed at hospital level to provide CAR-T therapies, a targeted grey literature review was performed with the aim of identifying the different clinical pathways of a patient during the administration of these therapies.

Next, nine qualitative interviews were conducted with members of the GETH-TC and key personnel involved in CAR-T management at qualified hospitals. They were asked about the resources required for the administration of CAR-T therapies at each phase of the journey of the patient, focusing on the three proposed patient scenarios (10/25/50). The results were validated with the SC to build the resource model. The criterion for the centres was that they were centres authorised in Spain to provide CAR-T therapies designated by the MoH. Interviews were conducted from 23 October to 25 November 2019.

### Participants

#### Interviews

Of the total number of centres designated by the MoH for the use of these therapies at the moment of the study (eight for adult patients and three for paediatric patients), eight participated in this phase. Hospital Universitario 12 de Octubre of Madrid was included in this phase due to its experience in the use of CAR-T therapy in the context of clinical trials (table 1).

Participants were contacted via mail to conduct the qualitative interviews, and the interviews were performed via telephone and lasted approximately 30 min. To minimise human error in data entry, interviews were recorded, extraction was reviewed by a second member of the team and then the recordings were deleted.

Table 1 Qualified hospitals designated by the MoH and hospitals included in the study

| AACC | Qualified hospitals | Hospitals included in the study |
|---|---|---|
| Castilla y León | Complejo Asistencial Universitario de Salamanca | Complejo Asistencial Universitario de Salamanca |
| Cataluña | Hospital Clinic Barcelona | Hospital Clinic Barcelona |
| | Hospital Universitario Vall d'Hebron | Hospital Universitario Vall d'Hebron |
| | Hospital Sant Joan de Deu | – |
| | Instituto Catalán de Oncología (ICO) Hospital Duran i Reynals | – |
| | ICO Hospital Germans Trias i Pujol | – |
| | Hospital de la Santa Creu i Sant Pau | Hospital de la Santa Creu i Sant Pau |
| Madrid | Hospital Universitario Gregorio Marañón | Hospital Universitario Gregorio Marañón |
| | Hospital Universitario Infantil Niño Jesús | Hospital Universitario Infantil Niño Jesús |
| | Hospital Universitario La Paz | – |
| | | Hospital Universitario 12 de Octubre |
| Valencia | Hospital Clínico Universitario de Valencia | Hospital Clínico Universitario de Valencia |
| | Hospital Universitari I Politècnic La Fe | Hospital Universitari I Politècnic La Fe |
| Andalucía | Hospital Universitario Virgen del Rocío | – |
| Canarias | Hospital Universitario de Gran Canaria Dr Negrín | – |

AACC, Autonomous Communities; MoH, Ministry of Health.

The structure of these interviews was based on the different phases of the CAR- T process, defined as: (1) phase 1, pre-apheresis; (2) phase 2, leukapheresis (sample extraction, preservation, delivery, reception and conditioning of the sample); (3) phase 3, lymphodepletion therapy; (4) phase 4, infusion and hospitalisation; (5) phase 5, follow-up. In the interviews, participants were asked about the resources needed at each phase of the process in terms of human resources, hospital infrastructure and machinery (online supplemental table 2).

## Data analysis

The hospital readiness to provide CAR-T was defined through an algorithm based on capacity and capability of the hospital and validated by the GETH-TC SC for this project and the GETH-TC board (figure 1). Then, the percentages defined in the algorithm were applied to the answers of the participants in the interviews in order to define the readiness of the hospital.

In this algorithm, capacity accounted for 65% of hospital readiness and was defined by: (1) total ICU capacity (25%); (2) total haematology and transplant unit capacity (50%) and (3) the capacity in the apheresis unit (25%).

On the other hand, capability accounted for 35% of hospital readiness and was defined by: (1) availability of a CAR-T team in the hospital (40%); (2) availability of a case manager in the hospital/haematology service (15%); (3) number of consultancy rooms (15%); (4) availability of social support (10%) defined by: (4.1) availability of social worker; (4.2) availability of specific haematology social worker; (4.3) capacity of access to welfare flats (high (>5 flats), medium (2–5 flats), low (1–2 flats), none (no capacity)) and (5) the nurse/patient ratio (20%).

The CART-T available capacity was calculated by considering: (1) the total capacity of the hospital, defined by the total number of beds available in the transplant unit, in

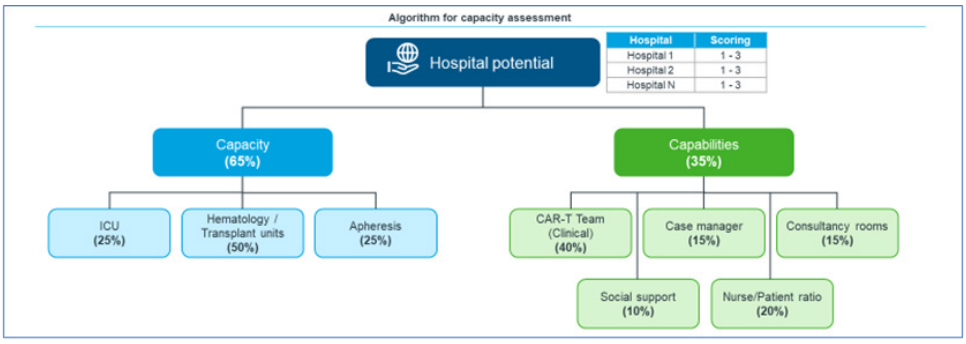


Figure 1 CAR-T available capacity. CAR-T, chimeric antigen receptor T cell; ICU, intensive care unit.

the haematology unit and in the ICU, and the number of machines available in the apheresis unit; (2) the occupancy, defined by the number of patients admitted in hospital, in haematology service and in the ICU in 2018 and the average length of stay of these patients; and (3) the average number of days of hospitalisation (30 days in the transplant unit and haematology unit, 4.5 days in the ICU and 4 hours in the apheresis unit) (online supplemental figure 2).

The capability was assessed through the participants' answers to a set of variables included in the algorithm and a weighting system applied to each variable status, ranging from 0 to 1, which was defined as: (1) availability of CAR-T team in the hospital (1 vs 0); (2) availability of case manager and/or administrative staff (1 vs 0); (3) number of consultancy rooms above average (1 vs 0); (4) availability of social support (1 vs 0); (5) nurse/patient ratio >1/4 (1 vs 0). Online supplemental figure 3 shows the points assigned according to the status of each assessed variable.

The percentages defined in the algorithm were then applied to the responses obtained from the participants in order to define the hospital's readiness.

Then, based on the hospital readiness results, the centres were grouped into three segments: segment A, which included the sites optimally ready, defined as having a hospital readiness between 70% and 100%; segment B, which included the hospitals somewhat ready, defined as having a hospital readiness between 40% and 70%; and segment C, which included hospitals not ready, defined as having a hospital readiness between 0% and 40%. Missing data on individual questions were managed by imputation with the mean value of the segment.

To quantify resources, three patient scenarios were defined on the basis of the estimated number of patients to be treated in a year, based on the estimated number of patients per month. Scenario 1 considered one patient per month and 10 patients per year; scenario 2, 2 patients per month and 25 patients per year; and scenario 3, 4 patients per month and 50 patients per year.

Then, to determine the resources needed by each hospital to provide CAR-T therapies in each patient scenario, a scoring programme was established, with 0 points representing the minimum response given by a hospital in the study and 3 points representing the maximum additional resources indicated as necessary by a hospital.

The results were not presented at hospital level to maintain anonymity and confidentiality. Non-response error was not considered, neither adjustment for non-representativeness of the sample.

**Table 2** Hospitals with a completion rate of more than 50% (final sample)

| AACC | Hospitals with a completion rate above 50% |
|---|---|
| Galicia | Complejo Hospitalario Universitario de Vigo |
| | Hospital Clínico Universitario de Santiago |
| Asturias | Hospital Universitario Central de Asturias |
| Cantabria | Hospital Universitario Marqués de Valdecilla |
| Navarra | Clínica Universidad de Navarra |
| | Complejo Hospitalario de Navarra |
| Castilla y León | Hospital Clínico Universitario de Salamanca |
| | Hospital Universitario Río Ortega |
| Aragón | Hospital Universitario Miguel Servet |
| Cataluña | Hospital Universitario Vall d'Hebron |
| | Institut Català d'Oncologia Hospitalet |
| | Institut Català d'Oncologia Badalona |
| | Hospital de Sant Pau Barcelona |
| Madrid | Hospital Universitario 12 Octubre |
| | Hospital Universitario Infantil Niño Jesús |
| | Hospital General Universitario Gregorio Marañón |
| | Hospital Universitario Fundación Jimenez Diaz |
| | Hospital Universitario Quirón Madrid |
| | Hospital de La Princesa |
| Valencia | Hospital Universitari I Politécnic La Fe |
| | Hospital Clínico Universitario de Valencia |
| Murcia | Hospital Clínico Universitario Virgen Arrixaca |
| | Hospital General Universitario Morales Meseguer |
| Andalucía | Hospital Regional Universitario de Málaga |
| | Hospital Universitario Virgen del Rocio |
| | Hospital Universitario Virgen de las Nieves |
| | Hospital Universitario Reina Sofia |
| Baleares | Hospital Universitari Son Espases |
| Canarias | Hospital Universitario de Gran Canaria Dr Negrín |

AACC, Autonomous Communities.

## Patient and public involvement

None.

## RESULTS

### Results of the first assessment: quantification of the current capacity of Spanish centres to administer CAR-T therapies

Of the 40 hospitals that were invited to participate, 32 finally responded to the survey and were considered as the initial sample for the study (online supplemental table 3). Table 2 shows the hospitals finally considered.

The completion rate for all hospitals in the sample was 57% (range 0–96%). Considering hospitals with a completion rate of more than 50%, the completion rate was 78% (range 54–96%). The final results show that the greatest differences among hospitals are caused by the high variability in the capacity index (figure 2).

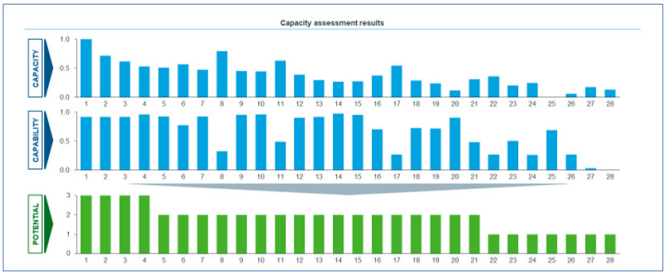


**Figure 2** Capacity assessment results.

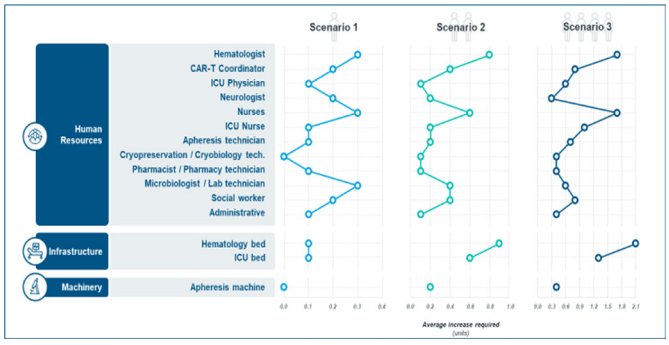


**Figure 3** Main results of the resource quantification assessment for the three patient scenarios. CAR-T, chimeric antigen receptor T cell; ICU, intensive care unit.

In an interim analysis of 28 out of 40 hospitals, hospitals were segmented into three groups (0–100% ratio scale) based on their readiness, determined by their capacity and capability. Four hospitals were included in segment A, 17 in segment B and 7 in segment C.

Extrapolating these results to 7 of the 14 centres currently designated for the administration of CAR-T and considering that it is a theoretical estimation based on 30-day hospitalisation, it can be observed that the current extrapolated capacity of the designated CAR-T qualified sites would allow to treat 250 yearly patients approximately.

### Results of the second assessment: identification and quantification of the different requirements/resources at hospital level to provide CAR-T therapies

Results of the resource quantification assessment show that human resources (haematologists and nurses) and beds are the most limiting factors and are the ones that require the most growth when the number of CAR-T patients increases. These results also highlight CAR-T coordinators as a key resource. The mean reference values for these resources based on responses from the participants were the availability of 1 physician for approximately every 38 patients per year, the availability of 1 nurse for every 3.4 patients per year and 15.1 patients per year with the possibility to be assigned per bed (haematology or ICU beds).

Results show that resources such as machinery were not considered a limiting factor for treating CAR-T patients and that social worker is a resource already overloaded in many hospitals.

Current CAR-T hospitals can manage approximately up to 12 yearly patients with no additional resources, but from 25 patients onwards, extra resources will be demanded (figure 3).

Also, it is important to bear in mind that some hospitals have already available quantity of resources to treat CAR-T patients (eg, Vall d'Hebron) that results in very few incremental resources in any of the scenarios considered.

## DISCUSSION

CAR-T therapies have emerged as an effective treatment option for patients with refractory or relapsed DLBCL and B-ALL who cannot undergo transplantation or who relapse after it. Clinical trials and real-life evidence have shown high response rates and durable remissions.[2 3 7 9] However, these therapies can induce potentially fatal adverse events, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[3 10 16] These toxicities have resulted in a significant number of patients requiring ICU admission. Therefore, the administration of CAR-T therapies necessitates not only adequate spaces and equipment for collection, processing, testing, cryopreservation and storage of the cellular product but also a comprehensive training of personnel, including ICU staff and neurology specialists.[10 17]

For these reasons, in Spain, these therapies were initially authorised only in specific centres designated by the MoH, based on pre-established criteria: (1) having a multidisciplinary unit formed by the professional involved in the process; (2) total activity of allogeneic transplants of complex haematopoietic progenitors in the last 3 years (2016–2018) of at least the 50th percentile; (3) having JACIE-CAT-ONT accreditation; (4) having recognition as national reference unit by the MoH of paediatric allogeneic HSCT; (5) having a multidisciplinary clinicopathological committee for the review of CAR-T drug candidates; (6) having clinical experience with CAR-T drugs in clinical trials; (7) having a certificate of compliance with the Spanish Agency for Medicinal Drugs standards of good manufacturing practice; (8) total haematopoietic progenitor apheresis activity in the last 3 years (2016–2018) of at least the 50th percentile; (9) total complex cell processing activity in the last 3 years (from the centre or reference progenitor bank) (2016–2018) of at least the 50th percentile; and (10) preclinical experience with immunoeffector cells.[18] The initial number of designated centres was established based on foreseen number of patients who would be appropriate candidates to CAR-T and capacity declared by those centres before the initiation of the programme without specific criteria.

However, meeting these criteria does not ensure that hospitals can take on the extra work that the initial number of CAR-T treatments entailed, much less the foreseeable increase in the coming years. In addition, the JACIE standards for immunoeffector cells establish that sufficient spaces, equipment and personnel must

be available. Experience in haematopoietic transplantation allows for an approximation, but neither JACIE nor scientific societies have established whether adequate resources in transplantation are also adequate for the use of CAR-T therapies. This project aimed to establish an objective methodology to inform about the adequacy of the Spanish health system, which could also be useful for other countries.

In Spain, as well as Italy, only a subset of the centres that fulfil the quality criteria for active CAR-T cell therapy use was effectively designated, while in France and Germany, all centres fulfilling national criteria were authorised by health authorities.[19] This fact could lead to differences in CAR-T capacity provision.

Although the results of the latest follow-up report show that so far, no overload has been detected in the designated centres, it shows that the number of requests has increased.[14] The increase in the number of requests, alongside the fact that the management of these therapies is complex and requires a large number of resources to handle their potential toxicity profile, and the complexity of the registries that have to be used to collect the data (VALTERMED and the EBMT registry), have led to an increase in the number of centres designated for the use of these therapies and the resources available in the currently designated.

This study was carried out with the aim of quantifying the resources needed to be able to treat patients with an adequate level of quality. To this end, an estimation was made regarding the degree of preparation required by potential centres in Spain to administer these therapies, as well as the resources that would need to be increased in the existing centres in the event of a rise in the number of patients to be treated per year.

Considering the increase in the number of requests, which accounted for a total of 497 in 2021 compared with 214 requests in 2020, and the results of the present study indicating that the estimated capacity of the current centres allows for the treatment of 250 patients per year, while only four of the potential centres would be optimally ready to administer these therapies with their current resources, it is important to start planning, investing and increasing resources. This is necessary to ensure the ability to continue providing this treatment. An increase in designated centres could be a preferred option over increasing capacity on selected centres to improve accessibility, as it would allow patients to access to a site closer to their home and minimise the bureaucracy of referrals between regions. Alternatively, centralised CAR-T therapies in selected centres would allow reducing learning curves and accumulating experience.

Despite the aforementioned reasons and the fact that these therapies consume and compete with the current hospital resources, no studies similar to the present one in Spain have been found that would allow for estimating the necessary resources and planning the potential increase of such resources and the number of centres, if necessary.

This study makes a first proposal for an objective way to quantify the capacity and resources needed to meet the demand for current and future CAR-T indications. As mentioned, one of the questions asked to the potential centres was whether they had JACIE accreditation. Of the 32 centres considered as the initial sample in this analysis, 16 had JACIE accreditation and 2 did not answer. This aspect is important since, in addition to being one of the criteria considered in the selection of centres in Spain designated by the MoH and able to use these therapies, it has been observed that its adoption is associated with improved survival outcomes, especially in allogeneic HSCT.[20]

However, in this study, it is important to consider that, for the capacity quantification, not all centres that perform allogeneic transplantation and could therefore be considered as potential centres for CAR-T administration completed the questionnaire. In the same way, not all centres that are designated for CAR-T administration participated in the interviews, so neither the estimation of capacity nor the estimation of resources needed has been made based on the total number of potential centres that were considered at the beginning.

Therefore, it is important to consider that expert opinion is useful to inform decisions in scenarios with high uncertainty. However, to confirm these results and provide more robust evidence that can promote the use of these alternatives, real-world practice and prospective studies would be necessary. These alternatives have demonstrated relevant results in the therapeutic approach of patients that actually represents an unmet need.

A first phase of an international registry-based risk-adapted benchmarking system for HSCT outcomes within EBMT has already been developed, using the experience of established national systems and methodologies achievable within the EBMT registry. The immediate objectives of this study were to deliver a performance benchmark report for the first phase to all EBMT member principal investigators, allowing them to compare the position of their centre with other anonymised EBMT centres in terms of follow-up completeness. This report aims to provide measurable outcomes for improvements in resource allocation, clinical supervision and education of data managers. This has been considered a road test for the next and more critical benchmark of survival outcomes. These types of studies may expand to include data reporting on non-transplant treatments, including CAR-T cells and other immune effector cells.[20]

## CONCLUSIONS

According to the results from this research, currently, the 14 CAR-T-designated hospitals (for adult and paediatric patients) have an estimated capacity of approximately 250 patients per year, below the current estimation of the MoH of approximately 400 CAR-T-eligible patients (339 with DLBCL and 68 ALL).

The most limiting factors for CAR-T administration were the availability of beds and human resources, haematologists and nurses.

In relation to these limiting factors, it can be seen that the need for these resources increases with the number of patients in each scenario. In scenario 1, defined by 10 patients per year, the number of additional resources required is zero; in scenario 2, defined by 25 patients per year, the number of additional resources both in terms of available beds, haematologists and nurses is approximately one extra resource; and in scenario 3, defined by 50 patients per year, the number of resources required continues to increase and is approximately two extra resources.

Increasing the number of CAR-T-qualified centres and/or increasing resources in the 14 current qualified sites are two potential strategies that could be envisioned to treat current and future CAR-T-eligible patients.

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