Title

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Ethical challenges with multiple myeloma BCMA CAR-T slot allocation: a multi-institution experience

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Abstract

CAR T cell therapies are FDA approved for patients with triple refractory multiple myeloma (MM). Real-world access to CAR T remains challenging due to supply chain limitations impacting manufacturing. The goal of this study was to evaluate the extent of this issue and how major

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centers are handling the challenges of CART manufacturing slot allocation. MM CAR T physician leaders at each CART treatment center across the US were surveyed. We received response from 17/20 centers. A median of one slot is allocated per month per center and the median number of patients per center on the waitlist since ide-cel approval was 20 (range 5–100). As a result, patients remained on the waitlist for a median of 6 months prior to leukapheresis (range 2–8). For patient selection, all centers reported using a committee of experienced CART physicians to ensure consistency. To ensure transparency, 15 centers make selection criteria, selection timeline and priority score readily available for CAR-T providers. Centers also reported using ethical values for selection: a) equal treatment: time spent on waiting list (n=12); b) priority to the worst-off: limited therapeutic options (n=14), MM burden (n=11), high comorbidity index (n=5); c) maximize benefit: most likely to complete apheresis (n=13) or infusion (n=13) or achieve response (n=8) and d) social value: younger pts (n=3). Maximizing benefit was considered the most important criterion by 10 centers. Our study is the first attempt to evaluate existing issues with MM CAR T access and the variability and challenges in patient selection. Integrating ethical resource allocation strategies, similar to the ones described here, into formal institutional policies would help streamline CAR-T access and protect the needs of both current and future patients and physicians

Keywords

CAR T cells; access; multiple myeloma

Introduction

Idecabtagene vicleucel (Ide-cel) chimeric antigen receptor T cell therapy (CAR-T) was approved by the FDA in March 2021[1] and ciltacabtagene autoleucel (cilta-cel) in February of 2022[2] for the treatment of refractory multiple myeloma (MM). The lifecycle of a myeloma CAR-T therapy includes 1) Product allocation and apheresis: Allotment of CAR-T slot to centers, baseline patient evaluation and cell collection which are stored and shipped to the manufacturing facility, 2) Product manufacturing: includes T cell activation, viral transduction, expansion and, in most cases, cryopreservation and 3) Product delivery to centers and 4) Lymphodepleting chemotherapy and product infusion. Since their approval, CAR-T therapies have faced several challenges limiting access to these products including the COVID-19 pandemic, staff shortages and fludarabine shortages. An additional major limitation includes technical challenges in manufacturing (viral vector shortages, more stringent regulatory definitions of “in-specification” products) that have restricted the timely delivery of these product. As a result, a limited number of CAR-T slots are allocated to certified treatment centers every month. These slots are not enough to meet existing patient demand which presents ethical and practical challenges for patient selection. The purpose of this study was to systematically evaluate the extent of this problem and to determine how major centers internally prioritize patients for CAR-T selection.

Methods

We surveyed one CAR T expert (director of MM and or CAR-T program) each from a total of 20 centers, selected for adequate geographical representation of the highest volume MM CAR-T centers across the U.S. The main survey was conducted prior to cilta-cel approval although a brief update was requested by centers after cilta-cel approval, that specifically asked centers to report a) how many slots they received per month (numeric response) for cilta-cel and b) how patients were selected for cilta-cel over ide-cel (free text response). The survey was designed based on existing literature on principles of ethical consideration of scarce medical resources allocation and was broadly composed of two sections to evaluate ethical challenges with CAR-T slot allocation[2]. The first section assessed current use and prioritization of ethical principles for slot allocation. The second section addressed organization and the process of patient selection. For several questions requiring a numeric answer, categories of ranges of values rather than absolute values were offered as possible responses. Participants were asked to utilize center data to answer the questions and were given a deadline of 30 days to complete the survey and the pooled results were analyzed after responses were received, on 1st March 2022. Statistical analyses were performed using descriptive statistics in Microsoft Excel.

Results

Seventeen out of twenty centers responded to the survey their distribution is shown in the Figure 1. The median year of earliest CAR-T infusion (SOC/trial) was 2017 (range 2010–2019). Fifteen centers treated more than 50 patients in 2021 with CAR-T cells for all indications (MM and other diseases); thirteen centers treated more than 50 patients in 2021 with MM (SOC/trial). These data suggest that most centers surveyed were high volume centers with experience administering these therapies. All centers reported no major decrease in CAR-T practice volume in the previous year, despite the COVID-19 pandemic.

A median of one ide-cel slot was allocated per month per center and 15 centers were allocated ≤ 2 slots per month (range 0 – 4/month/center). However, the median number of patients per center on the waitlist since ide-cel approval was 20 per month (range 5–100). As a result, patients remained on the waitlist for a median of 6 months prior to leukapheresis (range 2–8). When asked about potential outcomes of patients on the waitlist and given possible answers of approximately 0%, 25%, 50%, 75% and 100%, results reported across 14 centers showed approximately 25% of patients receive a leukapheresis slot for commercial CAR-T cells,25% enrolled on another non-CAR T clinical trial, 25% enrolled on CAR T clinical trials and approximately 25% of patients died or enrolled in hospice. These data underline the impact of current access limitations on patient care and outcomes.

Considering the access limitations above, we evaluated the factors utilized across centers to influence patient prioritization for these therapies. The most common criterion chosen was the availability of alternative therapy options, considered by 14 centers. The second most common criteria, both considered equally by thirteen centers were: a) considering favorably patients more likely to successfully undergo leukapheresis and b) to be dosed

with CAR T after leukapheresis. Twelve centers considered the time spent on the waitlist among their prioritization criteria, and 11 centers considered high disease burden as a prioritization criterion. Less commonly used criteria included: prioritizing patients more likely to achieve clinical response (used by 8 centers), prioritizing patients with higher comorbidity index (5 centers), social value (the example provided was a young patient providing for family versus an elderly retired patient) used by 3 centers, utilizing a lottery system (1 center) and selecting one patient per CAR-T clinician on a rotating basis (1 center). Next, since not all the selection criteria specified in the survey were considered with equal weights by centers when selecting patients, and since a core ethical principle could be represented my multiple selection criteria that in isolation may not have been most commonly selected by centers, we asked centers to rank the main core ethical values guiding their selection process. Maximizing total benefit (composite of patients most likely to make it to leukapheresis, and or dosing, and or clinical response) was the most commonly selected as most important among the four core ethical values (N=10), followed by treating people equally (described as time spent on wait list; N=7), giving priority to the worst off (limited to no treatment option left, N=6),and promoting social value as the least selected top priority (younger patient first, N=2). Interestingly, more than half of the centers reported that their prioritization of the values has changed based on their experience with manufacturing challenges including manufacturing failure and delays. Thus, priorities have shifted from prioritizing worse-off and treating patient equally to maximizing benefit. Of note, 4 centers did not use treating people equally and 6 centers did not use promote/reward social value at all in their prioritization of ethical values. The challenge is that with the prolonged waiting with CAR-T leukapheresis and manufacturing and the evolving access to other myeloma treatments, predicting patients most likely to make it to dosing and to have clinical response will be difficult.

To ensure consistency and inclusiveness of the patient selection/prioritization, 13 centers reported performing initial triage by a smaller, core team or triage officer (used by 2 centers) and 9 centers use a multidisciplinary team that includes MM experts, CAR-T physicians and may include ethicists, nurses, social workers and non-MM CAR-T physicians. Among the remaining 8 centers, physician-only teams decide on patient prioritization. To better understand the transparency of the patient prioritization process we inquired to whom the prioritization criteria for each case were made available to and who could attend the selection meeting. In 15 centers, the prioritization criteria are readily available to the treating clinician (referring and CAR-T specialist, when different). In 4 centers they were also available to patients and in 9 centers they were also available to other providers in direct care of the patient (e.g., nurses, advanced practice providers). In all centers, physicians in direct care of the patient were invited to attend the meeting and in one center, patients were also allowed to attend. Finally, 13 centers provided formal ranking scores for each patient on the waiting list, which were always available to physicians in direct care of the patient. To ensure accountability of the prioritization process, the prioritization scores, when applicable, were documented and tracked monthly in 9 centers that implement formal ranking. In 14 centers, a formal CAR-T quality program is in place to track and review the waiting list records and ensure patient selection is compliant with the formal process implemented by each center.

Since cilta-cel was approved for MM shortly after the completion of the initial survey, we asked centers in October of 2022, how many slots they received per month for cilta-cel and how patients were selected for cilta-cel over ide-cel. Fifteen of 17 centers responded. The median number of monthly cilta-cel slots was 2 (range 1–4). All centers reported that physician and patient preference was the most common factor influencing the decision to prescribe one product over the other. Five centers reported that longer manufacturing times for cilta-cel also influenced their decision on which product to prescribe according to the clinical scenario, but no center reported the use of formal criteria for patient allocation to each product.

Finally, we asked centers to comment (free text entries) on how their experience with commercial CAR-T has impacted their overall practice patterns and perception of this therapy. Noteworthy comments included:

> "This makes it even harder when I have patients dying off our list that we couldn't get this therapy to in time."
>
> "Some patients are delaying or refusing other treatment options including good clinical trials because of the focus on wanting CAR-T therapy and concern that they may become ineligible for future CAR-T treatment."
>
> "Commercial CAR-T has become the last resort."
>
> "…very difficult to justify who gets the 'golden ticket' and who does not…. This is affecting our mental health for the those of us taking care of these patients."

Discussion

In this study we provide the first in-depth review of CAR T slot allocation procedures at centers across the country. We identify significant limitations in overall CAR T slot availability and delays in administration. We also shed light on the processes used across centers to fairly allocate this limited resource to patients that need it.

Indeed, a median wait of 6 months prior to leukapheresis can have significant implications for treatment decisions made in these heavily pretreated patients. Our results are in agreement with recently published data[3] that showed a median wait time of 4 and 5 months from addition to a waitlist to apheresis and infusion, respectively. The same authors showed that approximately 25% of patients die while on the CAR-T waitlist which is what we also demonstrated in our study. Overall, 40% of waitlisted patients made it to CAR-T infusion, which is better than the estimates provided in our survey (25%) although this discrepancy may have to do with the survey methodology used that allowed only ranges of numeric responses to be used rather than raw data. Finally, they showed that younger patients and patients who had previously received a stem cell transplant were more likely to get to CAR-T infusion, which aligns with the "maximizing total benefit" value (composite of patients most likely to make it to leukapheresis, and or dosing, and or clinical response) in our study, since younger and more fit patients likely fared better when considering this ethical value.

Our findings highlight the need for early consultation with a CAR-T center by referring clinicians in the community, ideally before receiving 4 lines of therapy and/or developing triple refractory disease to minimize additional delays after the patient fulfills FDA label criteria for administration. This strategy will also allow for early planning of bridging therapy strategies while awaiting approval for CAR-T therapies, T cell apheresis or CAR-T infusion.

As a result of the availability limitations outlined here, we found that all centers had implemented internal prioritization strategies for CAR T allocation. Despite significant heterogeneity across centers, maximizing total benefit, which was the composite of patients most likely to make it to leukapheresis, and/or dosing, and/or achieve a clinical response, was the most heavily weighed criterion across most centers for patient selection.

The major limitation of our study was the use of a survey methodology. However, most centers surveyed responded and all centers surveyed were major referral centers across the US.

None of the ethical principles that we tried to evaluate in this study are sufficient on their own for just allocation of scarce medical resources. UNOS is a point-based system for organ allocation in the USA which is based on the core ethical values of treating people equally, giving priority to the worst-off and maximizing total benefit[4]. Similarly, a multi-ethical framework was defined during the COVID-19 pandemic for rationing of medical resource ethically[5]. Other centers have implemented formal scoring strategies for CAR-T allocation. The Cleveland Clinic utilizes a clinical factor system for slot allocation, which weighs disease refractoriness, aggressiveness of relapse, the need for bridge therapy, lack of alternative effective therapies and patient's life-expectancy[6]. CAR-T prioritization processes could be formally or informally modeled after these frameworks. More products and alternative manufacturing approaches may improve access in the future, but access issues are likely to remain an issue for the foreseeable future. Integrating ethical resource allocation strategies, similar to the ones described here, into formal institutional policies would help streamline CAR-T access and protect the needs of both current and future patients and physicians. Unfortunately, reaching consensus across institutions will remain a challenge in the foreseeable future. This is due to the complex clinical decision-making involved in the selection of each patient, the different decision-making structures and processes and the dynamic and variable allocation of slots, across institutions, as well as an ever-changing field with the approval of alternative options (e.g. bispecific antibodies), improvement in manufacturing workflows, availability of new CAR-T products or updated indications for existing products.

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Declaration of Competing Interest

Yi Lin disclosed the following: Consultant for: Kite/Gilead, Celgene/BMS, Juno/BMS, BlueBird Bio, Janssen, Legend BioTech, Gamida Cells, Novartis, Iovance, Takeda, Fosun Kite, Pfizer, Grant/Research Support from: Kite/Gilead, Celgene/BMS, BlueBird Bio, Janssen, Legend Biotech, Merck, Takeda, Boston Scientific. DSMB:

Sorrento. Data Review Committee: Pfizer. Scientific Advisory Committee: NexImmune. Sarah Holstein disclosed the following: Consultant for: BMS/Celgene, Janssen, Oncopeptides, Sanofi, Secura Bio, Takeda and Research funding from: BMS/Celgene, Oncopeptides. David S. Siegel discussed the following: Honoraria from Amgen, Takeda, Karyopharm, Jansen, and GSK. Speakers Bureau: BMS, Jansen, and GSK. Membership on entity's Board of Directors or advisory committees: Celularity. Sikander Ailawadhi disclosed the following: Consultant: GSK, Sanofi, BMS, Takeda, Beigene, Pharmacyclics, Amgen, Janssen Astra Zeneca, and Regeneron. Research funding: GSK, BMS, Pharmacyclics, Amgen, Janssen, Cellectar, Xencor, Abbvie, Medimmune, and Ascentage. Leif Bergsagel disclosed the following: Consultant for Pfizer, Janssen, and Oncopeptides.

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Highlights

- A small number of myeloma CAR-T slots are available due to manufacturing and other issues
- In our survey of 20 centers, patients waited an average of 6 months for CAR-T infusion
- About a quarter of patients died while waiting for CAR-T
- Patients more likely to make it to infusion and have a response were more likely to be selected for CAR-T therapy.

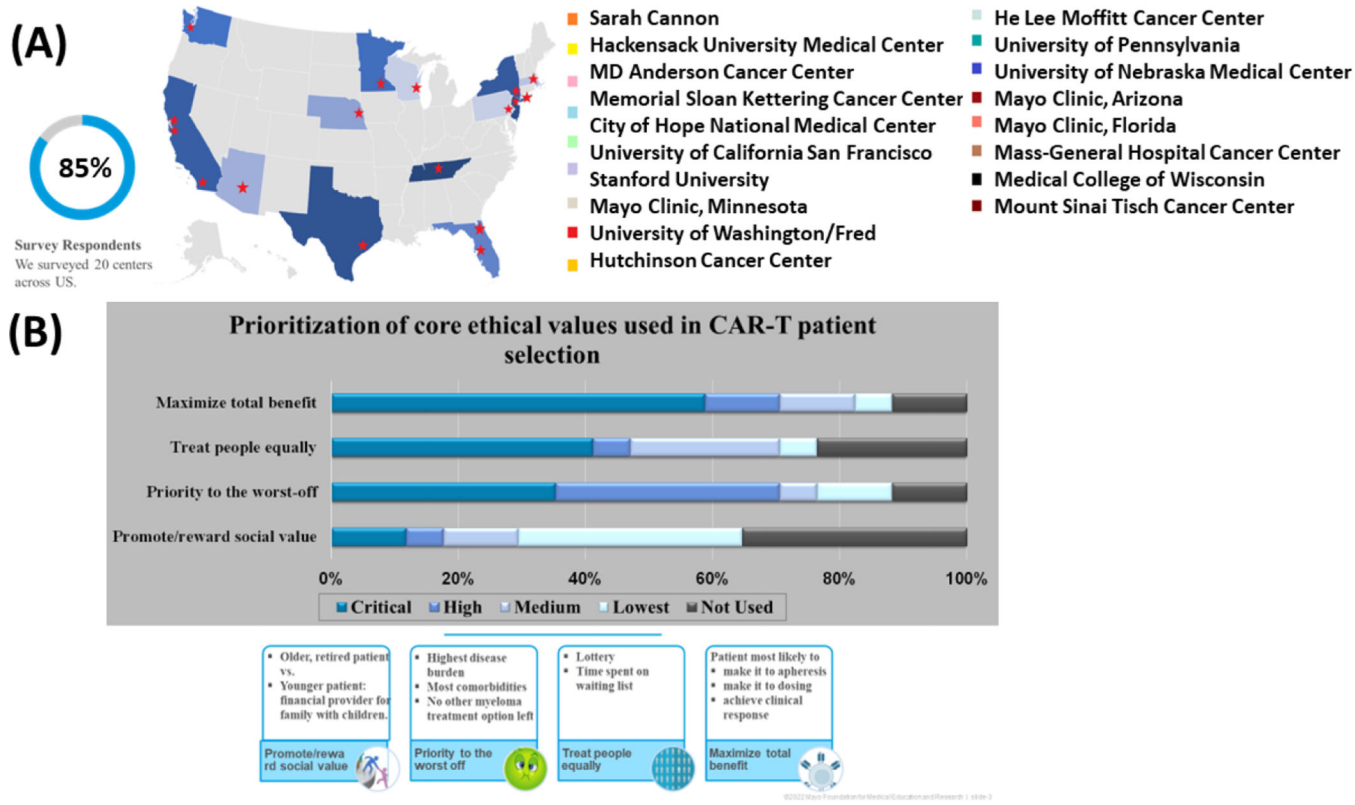

Figure 1:

(A) US map shows participating centers for CAR-T survey. We surveyed one CAR T expert (nominated by their respective MM groups) per center of excellence, defined as centers participating in the registration studies for ide-cel and actively administering CARTs, (B) Figure shows the simple ethical principles of CAR-T slot allocation which embody the core values. Bar graph shows prioritization of core ethical values used in CAR-T patient selection from highest to lowest as a percent of total survey respondents,