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Authors

Kim, Myung S
Cai, Johnny
Maniar, Ashray
et al.

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RESEARCH LETTER

Comparison of Classification of Indications for Allogeneic and Autologous Transplant for Adults in ASTCT Guidelines and Evidence Available in Published Literature

Hematopoietic stem cell transplantation (HCT) is a common procedure, with 22 000 cases performed in the US per year at a total cost of 1.3 billion dollars per year.[1] To our knowledge, an evaluation of the quality and level of evidence of society guidelines in HCT has not been performed. In the 1980s, oncologists adopted autologous stem cell transplant for metastatic breast cancer following high-dose chemotherapy based on uncontrolled studies only to find no clinical benefit in randomized clinical trials (RCTs).[2,3] In this study, we seek to quantify the number of RCTs in the literature for each indication by disease type and status. We then describe the published literature of the past 5 years.

Supplemental content

Methods | We reviewed evidence according to the American Society for Transplantation and Cellular Therapy (ASTCT) 2020 guidelines[4] for indications with S (standard of care) or C (clinical evidence available, standard of care) level recommendations for hematologic malignant diseases. Randomized clinical trials published in peer-reviewed journals were identified using the Ovid MEDLINE database. All publications under relevant medical subject headings (MeSH) were combined with results from keyword "transplantation" using the Boolean operator "AND." We limited the search to RCTs. We reviewed all articles from 2016 to present using Google Scholar by searching disease type and keyword "transplantation" (eTables 1 and 2 in the Supplement). We reviewed the first 100 results of each search. This study was exempt from institutional review board approval because it involved publicly available data and did not involve individual patient data.

Results | In total there are 103 recommendations in the ASTCT 2020 guidelines for allogeneic transplant and autologous transplant.[4] For allogeneic transplant, there are 43 S indications and 27 C indications. For autologous transplant, there are 23 S indications and 18 C indications. There were 4 RCTs for allogeneic transplant and 24 RCTs for autologous transplant corresponding to 3 and 11 S indications and 1 and 6 C indications for allogeneic and autologous transplant, respectively (**Table** and **Figure**).

In the published literature since 2016 in allogeneic transplant, we found 299 observation or nonrandomized interventional studies, of which 208 (70%) were single-arm studies. For autologous transplant, there were 156 observational or nonrandomized interventional studies, of which 87 (56%) were single-arm studies. The number of RCTs were none for allogeneic transplant and 4 for autologous transplant.

Discussion | In this review of the literature, we found that only 4 of 70 (6%) standard-of-care recommendations for allogeneic transplantation and 17 of 41 (41%) for autologous transplantation were supported by randomized clinical trials. Yet of 103 ASTCT indications there were 70 S and C recommendations for allogeneic transplant and 41 for autologous transplant. Taken together, our results demonstrate that there has been widespread adoption of HCT, especially allogeneic transplant, based on low levels of evidence.

Allogeneic transplant has now become standard of care by historical precedent for hematologic malignant diseases with poor prognosis, such as high-risk acute myeloid leukemia. Ethics and feasibility are raised regarding RCTs in this setting. However, offering an unproven aggressive therapy with high treatment-related mortality merely on the basis of poor predicted outcome is also questionable. Physicians may underestimate the burden of treatment and treatment complications and equate higher response rates or feasibility with longer survival or higher cure rates. These components should be explored formally in RCTs. This study is limited as it is not a comprehensive review of evidence for specific disease types. Instead, we aimed to provide an overview of the broad literature behind stem cell transplant.

The benefits of allogeneic transplantation are unknown in both highly lethal conditions such as plasma cell leukemia and less dismal conditions such as peripheral T-cell lymphoma. However, it would be more feasible to do pragmatic RCTs when there is clinical equipoise. Intermediate-risk acute myeloid leukemia is an example where retrospective studies are conflicting, and a pragmatic RCT is feasible. Randomizing transplant-

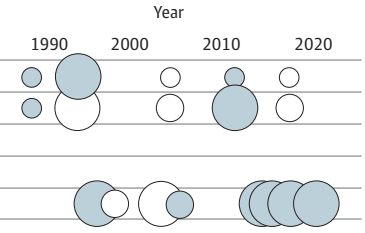
Table. S and C Indications for Allogeneic and Autologous Transplant With vs Without Published RCTs

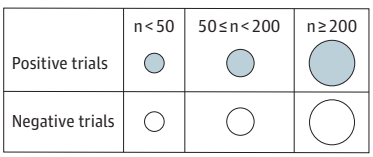
	No. (%)			
Indication	RCT	No RCTs	Total	RCT participants, No. (range)
Allogeneic				
S	3 (7)	40 (93)	43	96 (44-161)
C	1 (4)	26 (96)	27	138
Autologous				
S	11 (48)	12 (52)	23	75 (4-1197)
C	6 (33)	12 (67)	18	40 (3-425)

Abbreviations: C, clinical evidence available, standard of care; S, standard of care; RCT, randomized clinical trial.

Figure. Evidence Map of Randomized Cliniical Trials for Autologous Transplant Standard of Care Recommendations

Disease type	Disease status	Recommendation
Acute myeloid leukemia	CR1, low risk	C
	CR1, intermediate risk	C
	CR2	C
Acute promyelocytic leukemia	CR2, molecular remission	S
Plasma cell disorders	Myeloma, initial response	S
	Myeloma, sensitive relapse	S
	Myeloma, refractory	C
	Plasma cell leukemia	C
	Amyloid light-chain amyloidosis	S
	POEMS syndrome	C
	Relapse after autologous transplant	C
Hodgkin lymphoma	Primary refractory, sensitive	S
	First relapse, sensitive	S
	Second or greater relapse	S
Diffuse large B-cell lymphoma	Primary refractory, sensitive	S
	First relapse, sensitive	S
	Second or greater relapse	S
High-grade B-cell lymphoma, with *MYC* and *BLC2* and/or *BLC6* rearrangements	CR1 (PET negative)	C
	Primary refractory, sensitive	C
	First relapse, sensitive	C
	Second or greater relapse	C
Primary CNS lymphoma	CR1/first partial remission (consolidation)	C
	Relapse, sensitive	C
Follicular lymphoma	Primary refractory, sensitive	S
	First relapse, sensitive (including POD24)	S
	Second or greater relapse	S
	Transformation to high-grade lymphoma	S
Mantle cell lymphoma	CR1/first partial remission	S
	Primary refractory, sensitive	S
	First relapse, sensitive	S
	Second or greater relapse	S
T-cell lymphoma	CR1/first partial remission	S
	Primary refractory, sensitive	S
	First relapse, sensitive	S
	Second or greater relapse	C
Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia	Primary refractory, sensitive	C
	First or greater relapse, sensitive	S
Burkitt lymphoma	First or greater relapse, sensitive	C
Cutaneous T-cell lymphoma	Relapse	C
Plasmablastic lymphoma	Relapse	C
Chronic lymphocytic leukemia	Transformation to high-grade lymphoma	S





C, Indicates clinical evidence available, standard of care; CNS, central nervous system; PET, positron emission tomography; S, standard of care. Positive and negative trials for standard of care recommendations (S and C) in autologous transplantation are represented as circles. Size represents number of participants and are organized by date of publication and indication by disease type and status.

eligible patients at time of diagnosis with minimal restrictions on donor choice or induction regimens in both transplant and nontransplant cohorts would provide crucial information for informed decisions in patient care.

Myung S. Kim, MD
Johnny Cai, DO
Ashray Maniar, MD
Thomas Kartika, MD
Alyson Haslam, PhD
Vinay Prasad, MD, MPH

Author Affiliations: Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland (Kim); Division of Internal Medicine, Oregon Health and Science University Portland (Cai, Kartika); Division of Hematology Oncology, Columbia University, New York, New York (Maniar); Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco (Haslam, Prasad); Department of Medicine, University of California, San Francisco, San Francisco (Prasad).

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Corresponding Author: Vinay Prasad, MD, MPH, University of California, San Francisco, 550 16th St, San Francisco, CA 94158 (vinayak.prasad@ucsf.edu).

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Concept and design: Kim, Maniar, Prasad.
Acquisition, analysis, or interpretation of data: Kim, Cai, Maniar, Kartika, haslam.
Drafting of the manuscript: Kim, Cai, Kartika.
Critical revision of the manuscript for important intellectual content: Kim, Maniar, haslam, Prasad.
Statistical analysis: Maniar.
Supervision: Prasad.

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Guaranteed Financial Incentives for COVID-19 Vaccination: A Pilot Program in North Carolina

Uptake of the COVID-19 vaccine remains too low in the US as COVID-19 variant cases and hospitalizations continue to rise. Nudges that remove barriers and facilitate action can increase vaccine uptake.[1] Many states, North Carolina included, have announced incentive programs to motivate COVID-19 vaccination, including lotteries for $1 million.[2] However, these large but uncertain financial prizes benefit only a few lucky winners and do not broadly address access barriers to vaccination.[3,4] In contrast, guaranteed small financial incentives can offset costs related to lost wages, transportation, and childcare.

Supplemental content

Methods | This quasi-experimental study used a 2-week pilot incentive program that guaranteed a $25 cash card to adults who either received or drove someone to receive their first dose of COVID-19 at participating sites in 4 counties in North Carolina. Drivers could earn $25 for each trip but were not paid twice for the same trip (eg, receiving a vaccine while also bringing someone else). The pilot program distributed 2890 cash cards to vaccine recipients and 1374 to drivers. Analyses of COVID-19 vaccine first doses used a difference-in-differences approach. A competing risk model included constant hazard functions for 3 defined competing events: being vaccinated at (1) intervention sites, (2) elsewhere in the same 4 counties, and (3) elsewhere in the state. For each event, the model compared different hazards for 2 baseline periods (April 28-May 11, 2021, and May 12-25, 2021) with the intervention period (June 2-8, 2021); analyses censored the intervening pilot program week owing to staggered site launches in that week (eFigure 1 and eFigure 2 in the Supplement). The evaluation also characterized incentive recipients with a cross-sectional survey of vaccine recipients who received a cash card at the intervention sites.

Statistical analysis was performed from June 10, 2021, to August 27, 2021, using R, version 3.6.1 (The R Foundation for Statistical Computing). For the survey analyses, we used Stata, release 15.0 (StataCorp LLC). Tests were 2-tailed and statistical significance was set at $P < .05$.

The study's vaccine initiation analyses were approved by the institutional review board of the University of North Carolina at Chapel Hill, and its survey data collection protocol and analyses by the institutional review board of North Carolina Central University. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement reporting guidelines.

Results | Vaccine initiation analyses relied on data aggregated for clinics, thus data on patient race and ethnicity were unavailable. During the baseline periods, COVID-19 vaccine initiation increased in the intervention clinics (46.2%), declined elsewhere in the 4 counties (−9.5%), and increased elsewhere in the state (1.7%; all $P < .001$; **Table 1**). From the second baseline period to the intervention period, COVID-19 vaccine initiation declined less at sites offering the guaranteed financial incentive when compared with elsewhere in the same counties (−26.4% vs −51.1%) and the rest of the state (vs −48.6%; both difference-in-differences, $P < .001$).

Among 401 vaccine recipients surveyed (response rate, 92.4%; mean [SD] age, 41.8 [14.9] years; 207 [52%] women; 187 [47%] Black individuals), 41% reported the cash card was an