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Guideline

Updated Indications for Immune Effector Cell Therapy: 2023 Guidelines from the American Society for Transplantation and Cellular Therapy

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A B S T R A C T

The American Society for Transplantation and Cellular Therapy (ASTCT) published its guidelines on indications for autologous and allogeneic hematopoietic cell transplantation (HCT) and immune effector cell therapy (IECT) in 2020. Since then, we have witnessed rapid advancements in the field of IECT, resulting in several new chimeric antigen receptor T cell (CAR-T) products and disease indications being approved by the US Food and Drug Administration (FDA). To keep abreast of these practice changes, the ASTCT Committee on Practice Guidelines commissioned a focused update covering CAR-T therapy indications. Here we present updated ASTCT recommendations on indications for CAR-T therapy. Only FDA-approved indications for CAR-T were recommended and categorized as "standard of care," where the indication is well defined and supported by evidence. The ASTCT will continue to periodically review these guidelines and update them as new evidence becomes available.

INTRODUCTION

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines (CoPG) published a 5-year update to "Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation" that was broadened to include immune effector cell therapy (IECT) [1–4]. Because these guidelines serve as frequently cited, easy-to-use reference tools for referring and hematopoietic cell transplantation (HCT) physicians, as well as payers and policy makers, the need for periodic updates was emphasized to stay abreast of emerging relevant data. Considering the rapid scientific progress seen in IECT, specifically chimeric antigen receptor T cell (CAR-T) therapy, leading to multiple Food and Drug Administration (FDA) approvals of CAR-T products and indications in hematologic malignancies since 2020, the ASTCT CoPG has deemed it appropriate to provide a focused guidelines update for new CAR-T indications.

Notably, indications for autologous and allogeneic HCT have no new updates, and the reader is referred to a previous report [2]. Here we followed the general principles as described previously [2]. As noted earlier, these guidelines are intended not to determine the optimal therapeutic strategies for individual patients, but rather to possibly serve as a supervisory framework for patients, physicians, payers, and policy makers [1,2]. The FDA approval letters for each product and their respective indications were reviewed from the FDA website [5]. A formal systematic review of literature and grading on level of evidence was not attempted. FDA approval of

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additional disease indications for existing products and more IECT products for various diagnoses are anticipated in the future.

INDICATIONS FOR IECT

Of the plethora of IECT approaches under clinical investigation, these guidelines incorporate the most current FDA-approved CAR-T therapy indications. Table 1 lists approved products and the corresponding disease indications in children and adults. Brief descriptions of approved CAR-T indications by disease subtype are provided here.

Acute Lymphoblastic Leukemia

Two CD19-directed CAR-T products derived from autologous T cells have been approved by FDA to date. Tisagenlecleucel is approved for children and adults age ≤25 years with CD19-positive B cell acute lymphoblastic leukemia (B-ALL) that is refractory/resistant to therapy or in second or later relapse [6]. For adults (age ≥18 years) with B-ALL, brexucabtagene autoleucel is also approved [7].

Non-Hodgkin Lymphoma

For large B cell lymphoma, 3 CD19-directed autologous FDA-approved CAR-T products are available. Tisagenlecleucel is approved for adults with large B cell lymphoma that is relapsed or refractory after ≥2 lines of systemic therapy, including diffuse large B cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B cell lymphoma, and DLBCL arising from follicular lymphoma [8,9]. Axicabtagene ciloleucel is approved for adults with large B cell lymphoma that is

Table 1
Indications for IECT

CAR-T Product	Indication and Disease Status for Cellular Therapy	Pediatric (≤18 yr)	Adult
Axicabtagene ciloleucel	Large B cell lymphoma		
Target: CD19	Refractory to first-line chemoimmunotherapy*	NA	S
	Relapse within 12 months after first-line chemoimmunotherapy*	NA	S
	Large B cell lymphoma (DLBCL NOS, primary mediastinal large B cell lymphoma, high-grade B cell lymphoma, DLBCL arising from follicular lymphoma)		
	Primary refractory, resistant (after 2 lines of therapy)	NA	S
	Beyond second relapse	NA	S
	Relapse after autologous HCT	NA	S
	Follicular lymphoma*		
	Primary refractory, resistant (after 2 lines of therapy)	NA	S
	Beyond second relapse	NA	S
Brexucabtagene autoleucel*	Mantle cell lymphoma*		
Target: CD19	Relapsed or refractory	NA	S
	B-ALL*		
	Relapsed or refractory	NA	S
Ciltacabtagene autoleucel*	Multiple myeloma*		
Target: BCMA	Relapsed or refractory†	NA	S
Idecabtagene vicleucel*	Multiple myeloma*		
Target: BCMA	Relapsed or refractory†	NA	S
Lisocabtagene maraleucel*	Large B cell lymphoma (DLBCL NOS, high-grade B cell lymphoma, PMBL, and follicular lymphoma grade 3B)		
Target: CD19	Refractory to first-line chemoimmunotherapy	NA	S
	Relapse in ≤ 12 months of first-line chemoimmunotherapy	NA	S
	Relapse after first-line chemoimmunotherapy, ineligible for HCT	NA	S
	Primary refractory, resistant (after 2 lines of therapy)	NA	S
	Beyond second relapse	NA	S
	Relapse after autologous HCT	NA	S
Tisagenlecleucel	Acute lymphoblastic leukemia		
Target: CD19	Primary refractory or resistant (2 prior lines of therapy)	S‡	S‡
	Beyond second relapse	S‡	S‡
	Large B cell lymphoma (DLBCL NOS, high-grade B cell lymphoma, DLBCL arising from follicular lymphoma)		
	Primary refractory, resistant (after 2 lines of therapy)	NA	S
	First relapse, resistant to salvage therapy	NA	S
	Beyond second relapse	NA	S
	Relapse after autologous HCT	NA	S
	Follicular lymphoma*		
	Relapsed/refractory beyond 2 lines of systemic therapy	NA	S

NA indicates not applicable; S, standard of care; PMBL, primary mediastinal large B cell lymphoma; BCMA, B cell maturation antigen.
Only FDA-approved indications are shown. All IECT products are CAR-T products, listed in alphabetical order.

* Newer FDA-approved CAR-T products and indications, since 2020.

† After ≥4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

‡ Tisagenlecleucel is approved for all pediatric patients and adults up to age 25 years.

relapsed or refractory after ≥2 lines of systemic therapy, including DLBCL-NOS, primary mediastinal large B cell lymphoma, high grade B cell lymphoma, and DLBCL arising from follicular lymphoma [10,11]. Since the last update, axicabtagene ciloleucel has been approved for adults with large B cell lymphoma (DLBCL NOS and high-grade B cell lymphoma) that is refractory to frontline chemoimmunotherapy or that relapses within 12 months of the first line of chemoimmunotherapy [12]. Lisocabtagene maraleucel is now approved for adults with relapsed/refractory large B cell lymphoma after 2 or more lines of systemic therapy, including DLBCL NOS, transformed DLBCL arising from indolent lymphoma, high-grade B cell lymphoma, primary mediastinal large B cell lymphoma, and follicular lymphoma grade 3B [13], as well as for primary refractory disease and relapse within 12 months of first-line chemoimmunotherapy [14]. Indications for lisocabtagene maraleucel also include relapsed/refractory DLBCL after first-line chemoimmunotherapy (including relapses occurring >12 months from initial therapy) for patients ineligible for HCT due to comorbidities or age [15].

Since the last update, both tisagenlecleucel and axicabtagene ciloleucel have been approved for adults with follicular lymphoma that is relapsed or refractory to ≥2 lines of systemic therapy [16,17]. Brexucabtagene autoleucel is approved for treatment of adults with relapsed or refractory mantle cell lymphoma [18].

Multiple Myeloma

Idecabtagene vicleucel and ciltacabtagene autoleucel are autologous T cell-derived anti-B cell maturation antigen CAR-T products. Both products are currently FDA-approved for multiple myeloma that is relapsed or refractory to ≥4 lines of therapy that must include an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody [19–22].

CONCLUSION

Since the turn of this decade, several CAR-T products have been approved by the FDA for newer indications of therapy, as outlined above. The field of CAR-T therapy continues to expand rapidly. Real-life applications of these products relative to other available treatment options have been described in several recent ASTCT CoPG publications on treatment recommendations [23–25]. Studies exploring the use of CAR-T therapy earlier in the disease course are underway. The recently published KarMMa-3 trial reported better response and progression-free survival with idecabtagene vicleucel compared to standard of care in multiple myeloma patients after 2 to 4 previous lines of therapy [26]. The CARTITUDE-4 study, which compared ciltacabtagene autoleucel to standard of care in multiple myeloma patients after 1 to 3 prior lines, also met its primary endpoint of progression-free survival [27]. Similarly, potential approval for newer indications for existing CAR-T products (eg, lisocabtagene maraleucel in chronic lymphocytic leukemia [28]) are imminent. Emerging data for newer products, such as CD30-directed CAR-T for lymphoma [29], CD22-directed CAR-T for B-ALL [30,31], and bispecific CD19/CD22-directed CAR-T in for BALL and lymphoma [32], are currently experimental and appropriate in the setting of clinical trials. Alternative methodologies for CAR-T production and gene editing tools, such as CRISPR/Cas9, may allow for the immediate availability of off-the-shelf allogeneic CAR-T products and are currently being used in active clinical trials.

IECTs other than CAR-T, including chimeric antigen receptor natural killer cell (CAR-NK) [33,34], tumor-infiltrating T cell (TIL), T cell receptor, and cytokine-induced killer cell (CIK) therapies, are being explored in hematologic malignancies and solid malignancies such as germ cell tumor, sarcoma, neuroblastoma, and melanoma [35]. FDA approval has been sought for TIL therapy with lifileucel (LN-44) for treating patients with advanced or metastatic melanoma who progress after prior anti-PD-1/L1 therapy and targeted therapy [36]. Tabelecleucel is an allogeneic Epstein-Barr virus (EBV)-specific T cell immunotherapy approved by the European Medical Agency for patients age ≥2 years with relapsed/refractory EBV-positive post-transplantation lymphoproliferative disorder after at least 1 prior line of therapy [37]. The FDA has approved betibeglogene autotemcel, a novel gene therapy for transfusion-dependent β-thalassemia containing autologous CD34$^+$ hematopoietic progenitor cells transduced with lentiviral vector [38].

The foregoing examples illustrate the rapid advancements being made in cellular and gene therapy, and the CoPG plans to consider expanding the scope of these indication guidelines in future iterations. As more prospective and robust data demonstrate the safety and efficacy of IECT, it is anticipated that these recommendations will require critical review and regular updates.

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