blood advances

POINT CAR T cells better than BiTEs

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Despite significant advances in treatment regimens and outcomes in B-cell acute lymphoblastic leukemia (B-ALL), long-term survival remains poor for the 15% to 20% of pediatric patients and 50% of adults with relapsed or refractory (r/r) disease.[1-3] The emergence of immunotherapeutic strategies that use B-cell antigen–targeted single-chain variable fragments to direct T cells to specific surface antigens on B-ALL cells has revolutionized outcomes. These strategies include the US Food and Drug Administration (FDA)–approved bispecific T-cell engager (BiTE) blinatumomab and chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel.[4] Even though both therapies target CD19, outcomes vary significantly. We discuss considerations and potential benefits of the preferential use of CAR T-cell therapy over BiTE in r/r B-ALL, which can serve as a framework for evaluation of approaches with alternative antigen-targeting strategies.

Efficacy of CAR vs BiTE: response rates, trafficking, and durability

In the phase 2/3 trials leading to the FDA approval of blinatumomab in 2014, the objective response rate to blinatumomab in adult patients was 36% to 44%. Of those achieving a complete remission (CR), 63% to 88% had a minimal residual disease (MRD)–negative remission.[5-9] Importantly, of 70 pediatric patients evaluated, 39% achieved CR with only 14 (20%) being MRD negative.[10] Despite an improvement over responses with conventional salvage chemotherapy, as well as improved response rates for those with MRD-level disease,[11] results of the blinatumomab phase 2/3 and retrospective adult trials indicate that a significant portion of patients are resistant to blinatumomab (Table 1).[12]

In comparison, results from the ELIANA trial leading to FDA approval of tisagenlecleucel in pediatric and young adult B-ALL along with data from other CD19 CAR constructs support superior response rates with CAR T cells (Table 2). In these trials, CR rates have ranged from 67% to 100% with the vast majority achieving an MRD-negative remission.[13-21] For pediatric and young adult patients in particular, 81% achieved an MRD-negative remission with tisagenlecleucel by 3 months after infusion,[15] with comparable outcomes in adults who used the same construct,[22] also supported by the real-world experience.[23]

Furthermore, CAR T cells have demonstrated improved efficacy over blinatumomab in patients with both higher burden and extramedullary disease (EMD). Retrospective blinatumomab analysis found an inverse relationship between disease burden and response; only 29% of adults and 33% of children achieved a CR when bone marrow blasts exceeded 50%.[9,10] In comparison, the Seattle CD19 CAR trial showed no difference in CAR efficacy for patients with marrow blasts >25%.[17] Even when inferior outcomes were found with high-burden disease in the adult Memorial Sloan Kettering Cancer Center (MSKCC) trial, it only resulted in a decrease in CR from 95% to 75%.[14]

EMD at the time of treatment with blinatumomab has been shown to be an independent predictor of poor response, and EMD relapse after treatment seems to be a mechanism of resistance.[5,9] This is important, because more than 40% of patients with relapsed B-ALL have extramedullary involvement and 7.5% to 15% present with isolated central nervous system (CNS) disease.[1] CD19 CAR T cells have been shown to both eradicate CNS disease[17] and to have an antileukemic effect on other non-CNS EMD sites, including the ability to eradicate previously resistant EMD.[24,25] The inferior response seen with the use of blinatumomab, particularly in patients with high disease burden and those with EMD, including CNS involvement, may be partly a result of passive trafficking of BiTE therapy, which is reliant on recruiting endogenous T cells to interact with its target antigen.[4] This is in comparison with active trafficking and expansion of CAR T cells, which involves a highly dynamic, active process involving cell-cell interactions and signaling molecules resulting in chemotaxis of CAR T cells to sites of leukemia.[26] Given the lack of evidence that blinatumomab is able to cross the blood-brain barrier, it is not recommended for treating active CNS disease,[9] which limits its use and efficacy in those with CNS or other EMD involvement.

Table 1. Major clinical trials for blinatumomab

Study	n	Median age (range), y	CR,* %	MRD-CR, %	Relapse, %	RFS, median	OS, median
MRD pilot[50,51]	20	47 (20-77)	NA	80	50	5-y = 50%	NR
BLAST trial[52]	116	45 (18-76)	NA	78	43	18.9 mo	36.5 mo
Phase 2 pilot[5]	36	32 (18-77)	69	88	40	7.6 mo	9.8 mo
Phase 2 confirmatory[6]	189	39 (18-79)	43	82	46	5.9 mo	6.1 mo
ALCANTARA trial[7]	45	55 (23-78)	36	88	50	6.7 mo	7.1 mo
Phase 3[8]	271	41 (18-80)	44	76	NR	6-mo = 31%†	7.7 mo
Pediatric trial[10]	70	8 (<1-17)	39	52	56	4.4 mo	7.5 mo
City of Hope retrospective[9]	65	33 (7-74)	51	63	61	6.3 mo	NR

NA, not available; NR, not reported; OS, overall survival; RFS, relapse free survival.
*CR (complete remission) is inclusive of CR with count recovery, as well as CR with incomplete hematologic recovery and CR with incomplete count recovery.
†EFS (event-free survival).

CAR T cells also have the potential ability to engraft long-term, creating a constant pool of tumor-reactive T cells capable of surveilling and responding to disease recurrence before it is clinically evident.[4] This is in stark contrast to the very short half-life of blinatumomab, which necessitates a continuous infusion over a 28-day period for ongoing activity. Indeed, the biology of CAR T-cell expansion is related to having T cells that are fully directed at CD19 targeting, which is different from the more generalized polyclonal T-cell proliferation that may be induced by blinatumomab.[27] Indeed, CD19-directed CAR T cells have been shown to persist for up to 39 months after a single infusion,[15] and the ability to produce long-term engraftment has also resulted in a more durable response compared with that seen with blinatumomab. Patients successfully treated with blinatumomab achieved a shorter relapse-free survival (RFS) of 5.9 to 6.7 months with a median overall survival (OS) of 6.1 to 7.1 months.[5,7,8]

In addition, the majority of relapses have occurred during administration of blinatumomab or before planned consolidative allogeneic hematopoietic stem cell transplantation (HSCT). This is concerning because HSCT is essential for long-term survival when using blinatumomab, given the high-risk of relapse without HSCT.[9] In comparison, recent updates from the ELIANA trial found an RFS rate of 80% at 6 months and 66% at 12 and 18 months with evidence of functional CAR T-cell activity, given persistent B-cell aplasia.[28] Although CAR T cells can be used as a bridge to a consolidative HSCT, and may improve event-free survival (EFS) and OS,[16,18,19,29-32] it may not be essential for durable long-term remission in all patients, as opposed to treatment with blinatumomab. Antigen-negative escape is a frequent occurrence, seen in up to 20% to 30% of patients receiving either CD19 CAR T cells or blinatumomab[22,33] and will likely continue to be a mechanism of relapse with alternative single-antigen targeted strategies. Advances in combinatorial antigen CAR T-cell strategies may further optimize the potential for durable remissions above and beyond BiTEs as these novel constructs evolve.[34]

Safety: CRS, ICANS, and age-based tolerability

Toxicities associated with both these novel immunotherapies include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). This is of particular importance for older patients and their ability to tolerate severe CRS and ICANS, both of which occur more frequently with CAR T-cell therapy.[35] Furthermore, a benefit of blinatumomab is the ability to stop the infusion in response to toxicity, which is not

Table 2. Major clinical trials for CD19 CAR T cells

Study	n	Median age (range), y	CR,* %	MRD-CR, %	Relapse, %	EFS	OS
University of Pennsylvania/Children's Hospital of Philadelphia[13]	30	14 (5-60)	90	88	26	6-mo = 67%	6-mo = 78%
Memorial Sloan Kettering Cancer Center[14]	53	44 (23-74)	83	67	57	Median = 6.1 mo	Median = 12.9 mo
ELIANA trial[15]	75	11 (3-23)	81	81	36	12-mo = 50%	12-mo = 76%
National Cancer Institute[16]	21	13 (1-30)	67	86	14	5-mo = 79%†	10-mo = 52%
Seattle Children's Hospital[17]	45	12 (1-25)	93	100	45	12-mo = 51%	12-mo = 70%
Fred Hutchinson Cancer Research Center[18]	53	39 (20-76)	85	85	49	Median = 7.6 mo	Median = 20 mo
Hebei Yanda Lu Daopei Hospital[19]	51	11 (3-68)‡	90	88	24	NR§	NR§
		24 (2-44)¶					
City of Hope[21]	13	33 (24-72)	100	91	NR	NR	NR
CARPALL trial[20]	14	9 (1-19)	86	86	50	12-mo = 46%	12-mo = 63%

*CR (complete remission) is inclusive of CR with count recovery, as well as CR with incomplete hematologic recovery and CR with incomplete count recovery.
†LFS (leukemia-free survival).
‡Patients with r/r ALL.
§After HSCT: 6-month LFS, 81.3%; 6-month relapse rate, 11.9%.
¶Patients treated for MRD positive disease.

a possibility with CAR T cells. Although the increased risk of severe CRS (8.3% to 43% depending on CD19 CAR construct and grading system) remains a major concern with CD19 CAR T cells, early mitigation strategies with tocilizumab and/or corticosteroids that have not decreased CAR efficacy impaired engraftment or persistence or increased risk of serious infection[36] and improved the safety profile. Treating patients with low-burden disease (bone marrow blasts <5%) has also been shown to decrease the risk of both severe CRS (5% vs 41%) and neurotoxicity (14% vs 59%).[14]

In addition to its tolerability, in the small sample size of older adults treated on initial CD19 CAR trials, 75% (6 of 8) of r/r B-ALL patients older than age 60 years in the MSKCC trial responded to therapy, and a CR was achieved in all 4 older patients treated on the Fred Hutchinson Cancer Research Center (FHCRC) study.[14,24] The recently published TRANSCEND trial that used CD19-targeted lisocabtagene maraleucel in r/r non-Hodgkin lymphoma showed tolerability of CAR T cells in a predominately older (median age, 62 years), heavily pretreated, and chemotherapy-refractory population.[37] Thus, safety concerns for CAR T cells should not preclude consideration of this therapeutic modality in the elderly, which is all the more relevant in this population in which the potential for a durable response with CAR T cells may be highly desired, in part because of the concern for HSCT-related morbidity and mortality.

Feasibility: timing, manufacturing, and cost

Finally, a major criticism of CAR T cells is associated with therapy costs and time required to manufacture an individualized product. Despite the higher price of CAR therapy, an analysis comparing cost-effectiveness of tisagenlecleucel and blinatumomab, including subsequent HSCT based on historical rates, favored CAR T cells overall. This was driven primarily by the superior quality-adjusted life-years estimated for CAR T cells (11.26) compared with BiTE (2.25).[38] Advances in manufacturing, including implementation of automated manufacturing, point-of-care delivery,[39] and off-the-shelf strategies,[40] will lead to both lowered cost and improved accessibility in a timely manner, which will improve the feasibility of CAR T cells as a first-line strategy for those with r/r disease. In addition, advances in CAR T-cell engineering, including modifications to optimize safety (eg, incorporation of a safety switch) and/or efficacy will continue to evolve[41,42] and serve to improve the functionality and versatility of CAR T cells, which may not be as feasible with BiTEs.

Sequential therapy: considerations

Although this article is presented as a discussion on the merits of CAR T cells over blinatumomab in r/r ALL, in reality, both therapies can and are being used sequentially by patients. In particular, for those with more rapidly progressing disease, the ready availability of BiTEs may make it appealing to use first. However, providers must weigh the ease of access with the trade-off of the potential impact of blinatumomab on future therapies. Not only does blinatumomab therapy have inferior OS/EFS, particularly in those with high disease burden and EMD, it may decrease effectiveness of subsequent CD19 CAR T cells with modulation of both target and nontarget antigens.[43,44] Given that optimal CAR therapy is dependent on antigen density, prior BiTE therapy has the potential to diminish the efficacy and/or response durability of subsequent CD19 CAR T cells.[43,45]

Beyond B-ALL

The experience with alternative BiTEs and CAR T-cell strategies that extend beyond CD19 targeting is evolving. For instance, in multiple myeloma (MM), there are a host of emerging BiTEs as well as CAR T cells targeting several different MM antigens, including B-cell maturation antigen, CD38, and CD138, among others.[46-48] CD20 represents another attractive target for B-cell lymphomas, and certainly both CD20 targeted BiTEs and combinatorial CD19-CD20 CAR T-cell constructs[49] are actively being tested. Further experiences with these novel approaches will provide greater insight into the merits and limitations of CAR T cells vs BiTEs beyond B-ALL, but the framework set forth will likely apply.

In summary, we provide an overview of the benefit of CAR T cells over blinatumomab in the context of 2 FDA-approved agents for pediatric $CD19^{+}$ B-ALL. The ability of CAR T cells to more effectively traffic to EMD and tackle high-burden disease, in the context of ongoing improvements in the CAR T-cell safety profile, and potential for long-term remission make it a more appealing therapeutic strategy. How comparable strategies and considerations fare in diseases beyond B-ALL remain an active area of investigation.

Authorship

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