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CAR T cells: the missing piece needed to improve outcomes for children with cancer?

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ABSTRACT

B cell acute lymphoblastic leukemia (B-ALL) is the most common cancer of childhood. Outcomes for B-ALL have steadily improved over the last five decades, most recently due to impressive activity of chimeric antigen receptor modified T (CAR-T) cells and bispecific antibodies targeting CD19. In contrast, progress against other pediatric cancers has largely stalled. Significant academic effort is underway to expand the reach of CAR T cell therapy in pediatric cancer beyond B-ALL to other hematologic malignancies, solid cancers and brain tumors. Promising clinical activity using CAR-modified T cells has already been demonstrated in neuroblastoma and diffuse midline glioma by targeting the GD2 ganglioside, in pediatric sarcomas by targeting Her2, in Hodgkin's disease by targeting CD30, in T cell lymphoblastic leukemia by targeting CD5 or CD7, and in CAR19 refractory B-ALL by targeting CD22. Comprehensive surfaceome profiling of pediatric tumors is revealing additional novel candidate CAR targets expressed on pediatric cancers, including oncofetal cell surface antigens such as GPC2 and GPC3, which are expressed broadly on pediatric solid and brain tumors, and major histocompatibility complex bound peptides from oncofetal intracellular proteins such as *PHOX2B*. Next-generation CAR T cell therapeutics that incorporate suicide domains, regulatory circuits, logic gating and potency enhancements as well as combination immunotherapies are expected to further augment efficacy while maintaining safety. Current trials are administering CAR T cells in patients with refractory disease, but future studies are warranted to determine whether adjuvant use of CAR T cells could deliver cures with lower intensity standard therapy regimens and thereby reduce long-term toxicities in pediatric cancer survivors. Despite this scientific and clinical progress, the high cost of developing CAR T cells through the traditional biopharma pathway is limiting late-stage clinical development, necessitating the creation of new business models to commercialize CAR T cells for these small markets. CAR T cells hold great promise for improving outcomes for pediatric patients with cancer, but substantial additional research and clinical development is needed if this promise is to be realized for children afflicted with cancer.

Since the founding of the *Society for the Immunotherapy of Cancer* in 1984, treatment of adult cancers has undergone a metamorphosis, in large part due to immunotherapies that increase cures with less toxicity compared with cytotoxic chemotherapy and radiotherapy. Treatment of pediatric cancers over that same period tells a very different story. Cytotoxic chemotherapy remains the backbone of standard pediatric cancer regimens and radiation therapy is commonly employed. "Cures" delivered with these regimens come at the cost of lifelong late effects that increase in incidence and severity over time and dramatically reduce the healthspan and lifespan of survivors. Immunotherapy has the potential to increase cure rates and reduce the cost of cure in children, as it has in adults, but most immunotherapies optimized for activity in adult cancers are not active in pediatric cancers. Much work remains to be done if we are to realize the dream of delivering the "immunotherapy revolution" to children with cancer.

Differential responses of pediatric versus adult cancers to specific immunotherapies relate to fundamentally distinct pathways of oncogenesis. Adult cancers are typically induced by accumulated genetic mutations acquired over the course of years, while pediatric tumors occur as the result of a primitive cell with an embryonal milieu acquiring one or very few driver mutations. Pediatric cancers express many fewer genetic mutations compared with adult cancers, are classified as "cold" tumors and are largely resistant to checkpoint inhibitors.[1 2] In contrast, synthetic immunotherapies designed to induce de novo immune responses hold promise for treatment of pediatric cancer. Among these, chimeric antigen receptor T (CAR T) cells have shown significant activity in a remarkably wide range of pediatric cancers, spanning liquid, solid and brain tumors (table 1). These early results are providing hope that CAR T cell therapies could be the missing piece needed to improve survival rates while decreasing lifelong toxicity in childhood cancer survivors.

Table 1 CAR T cells with demonstrated clinical activity in pediatric cancers

Agent	Disease	Response rate	Selected references*
Tisagenlecleucel	R/R B-ALL	>80%	3
GD2.z-CAR	Refractory neuroblastoma	27% retained remission @ 18 years. f/u	11
GD2.BB.z-CAR	Diffuse midline gliomas	81% clinical and/or radiographic benefit	14
GD2.28.BB.z-CAR	Refractory neuroblastoma	63% CR, 29% PR	12
CD22.BB.z-CAR	R/R B-ALL	73% CR	5
CD30.28.z-CAR	Hodgkin's disease	59% CR, 13% PR, 9% SD	19
CD7.BB.z-CAR†‡	T cell acute lymphoblastic leukemia	85–90% CR	7 8
†CD5.BB.z-CAR‡	T cell acute lymphoblastic leukemia	100% CR	9
HER2.28.z-CAR	Sarcomas	21% CR, 29% SD	13
GPC3.BB.z-IL15-CAR	Sarcoma, Wilm's, hepatoblastoma	33% PR, 33% SD	16

*Due to space limitations, only selected references are included.
†Incorporated ER retention domains to prevent fratricide.
‡Pan *et al* used allogeneic CAR T cells.
B-ALL, B cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor.

In relapsed/refractory B cell acute lymphoblastic leukemia (B-ALL) resistant to all other standard therapies, CD19-CAR T cells induce remission in >80% of children[3] and cure approximately 30% of patients treated with high disease burden and 50% of children treated with minimal disease burden.[4] CD22-CAR T cells similarly induce very high remission rates in refractory B-ALL, including patients refractory to CD19-CAR.[5] The remarkably consistent and potent activity of CAR19 therapies in B-ALL fueled the early enthusiasm for CAR T cells as a therapeutic class, and tisagenlecleucel, a CD19.BB.z-CAR was the first CAR T cell to be approved for marketing by the US Food and Drug Administration. Tisagenlecleucel remains commercially available for patients ≤25 years with relapsed/refractory B-ALL for whom it has dramatically improved outcomes. Toxicity of CAR T cells for B-ALL has been relatively modest, since cytokine release syndrome and depletion of normal B cells are readily managed using standard supportive care. Thus far, long-term late effects of CAR T cells have been less severe than those observed following allogeneic stem cell transplantation and other intensive therapies previously used in this high-risk population.

CAR T cells also mediate significant response rates in T cell lymphoblastic leukemia (T-ALL), a disease that primarily afflicts adolescents and young adults. Results are most advanced for CAR T cells targeting CD5 and CD7, despite the significant challenges of fratricide, T cell aplasia and product contamination due to circulating T-ALL blasts. Fratricide resistance has been avoided via CD7-targeting endoplasmic reticulum retention tags and natural masking of CD5 due to rapid internalization that apparently prevents fratricide for this target.[6] Both CD7.BB.z- and CD5.BB.z--CAR T cells have shown high rates of activity for relapsed/refractory T-ALL, although additional work is needed to decrease relapse and opportunistic infections.[7–9] In contrast, progress using CAR T cells for acute myelogenous leukemia has been slow, due to the challenges of targeting antigens that are also expressed on vital hematopoietic cells as well as massive inter- and intrapatient heterogeneity of pediatric AML. The field awaits a breakthrough for CAR T cell treatment of AML as this remains a major cause of morbidity and mortality in children.

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood and only approximately 50% of children diagnosed with high-risk NB survive, despite very intensive standard therapy regimens. The earliest reported trial of CAR T cells for the treatment of cancer was a study of a first-generation CAR T cell targeting the GD2 ganglioside in children with refractory NB. Although expansion and persistence were low compared with that observed with current second-generation CAR T cells, outcomes were reported to be favorable.[10] A recent report evaluated patients 18 years following completion of this study, which demonstrated that among three of eight patients who had active disease at the time of treatment, two were sustained complete responders with follow-up at 8+ and 18 years. Of eight patients treated at high risk of recurrence in the original study, five remain disease-free 10–14 years from treatment.[11] These data provide the most mature follow-up of any solid tumor CAR T cell trial to date and lead to the conclusion that CAR T cell therapies are potentially curative for patients with solid cancers in general and NB in particular. A recent study also reported impressive outcomes for children with high-risk NB treated with a third-generation GD2-CAR T cell.[12] Together, the data provide compelling evidence that GD2-CAR T cells are active therapeutics for patients with high-risk NB that could enhance survival while reducing toxicity. Promising results with CAR T cells targeting Her2[13] and GPC3[12] have also been observed in pediatric patients with sarcomas and other pediatric solid cancers.

Very little progress has been made in the treatment of high-grade pediatric brain tumors in the last 40 years, which now kill more children in developed countries than leukemia. For H3K27M diffuse midline gliomas (DMGs), the largest killer of children with brain tumors, standard upfront treatment is limited to palliative radiotherapy and essentially all children die of their disease. Recently, massive overexpression of the GD2 ganglioside on DMGs was discovered and intravenous and intracerebroventricular GD2-CAR T cells demonstrated safety and significant activity in DMGs as measured by major tumor regressions, neurologic improvement and at least one case of sustained disease eradication.[14] These results are providing new hope for patients with H3K27M DMGs and children with other high-grade embryonal brain tumors. Based on exciting results in preclinical models, many clinical trials are now open globally to test CAR T cells for pediatric brain tumors, and the field anxiously awaits these results.

Many cell surface antigens prioritized for CAR targeting in pediatric cancers differ from those overexpressed on adult cancers, necessitating separate paths for development of CAR T cells in pediatrics versus adult cancers. The embryonal nature of pediatric solid tumors theoretically provides an opportunity to safely target oncofetal cell surface antigens. A prototype for this class of targets is the glypicans, with emerging promising preclinical and clinical data using CAR T cells targeting GPC2[15] and GPC3[16]. Recent preclinical data has also demonstrated activity of CAR T cells targeting major histocompatibility complex restricted expression of peptides derived from *PHOX2B*, an intracellular oncofetal target expressed in NB.[17] The field would benefit greatly from comprehensive cell surfaceome profiling to identify additional oncofetal or other targets that should be prioritized for CAR T cell therapy in pediatric cancers.

Clinical trials of CAR T cells for pediatric cancers have almost exclusively tested therapeutics that have not incorporated enhancements to endow multi-specificity, augmented T cell potency or persistence and these have been tested in patients with end-stage bulky disease. Based on the remarkable advances we are witnessing in cellular engineering, the field anticipates that next-generation platforms will augment the potency of this therapeutic class and enhance their safety, providing the opportunity for testing earlier in the disease course, and potentially in patients with lower tumor burdens. In addition, the field awaits studies of combinatorial regimens that incorporate cell therapies, either combining multiple immunotherapies or immunotherapies with targeted or cytotoxic therapies.

While the scientific and clinical progress in developing CAR T cells for pediatric cancers is impressive, the commercialization of these therapeutics has stalled. Indeed, the major challenge facing the field of cell-based immunotherapy for pediatric cancer relates to financial challenges that limit investment of biopharma in this space.[18] As a result, new business models are needed to bring cell therapies to market for pediatric cancers and any breakthrough that can reduce the cost of development will greatly accelerate progress. As cell manufacturing is the major cost driver for this therapeutic class, we anticipate that progress in developing bedside or in vivo manufacturing of cellular therapeutics for pediatric cancer could greatly accelerate the rate at which these novel therapeutics can ultimately be brought to market and thereby become available to all children who can benefit.

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