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**RESEARCH ARTICLE**
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# ASSESSING THE EFFECTS OF IMMUNOTHERAPY ON CHILDHOOD HEMATOLOGIC CANCERS

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**Abstract**

**Objectives:** The present paper is designed to assess the outcomes of immunotherapy as the approach to treat children diagnosed with hematologic cancer in Pakistan and China in terms of treatment outcomes, adverse immunotherapy-related manifestations, and survivals.

**Materials and Methods:** A postal cross-sectional study was carried out using data from different pediatric oncology centers in Pakistan and China. The sample design was immunotherapy children under 18 years having a hematologic cancer diagnosis from January 2018 up to December 2023. I only included patients who had undertaken at least one full cycle of immunotherapy. Outcomes from the treatment, adverse effects, and overall patient profile were evaluated over five years.

**Results:** The current study established that there was a wide variation in the treatment outcomes, with CAR T-cell therapy displaying the highest response rates to treatment, although it is accompanied by great risks like cytokine release syndrome (CRS) and neurotoxicity. Studies on the monoclonal antibody types revealed that they have a safer risk-thresh tone with equal therapeutic value. The more recent checkpoint inhibitors posed lesser side effects but were less efficient in the given cohort.

**Conclusion:** Immunotherapy has produced great success for pediatric hematologic cancers, each child requires an appropriate therapeutic plan for better outcomes while avoiding adverse effects.

**Keywords:** Pediatric hematologic cancers, immunotherapy, CAR T-cell therapy, monoclonal antibodies, checkpoint inhibitors, treatment outcomes, Pakistan and China.

## INTRODUCTION

Acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and lymphomas are some of the common childhood hematologic cancers. Translational treatments, including chemotherapy and radiation, have also increased survival this is accompanied by adverse effects and lifelong complications (1). Moreover, newer developments in immunotherapy seem to have a better deal in treating cancer cells than harming normal cells. Immunotherapies use the immune system to identify and obliterate malignant cells and offer better therapeutic prospects for pediatric cancer patients (2).

Immune therapy for childhood cancer remains a young science, with several strategies being developed and integrated into practice. Some well-known approaches include CAR T-cell therapy, immune-directed therapy, monoclonal antibodies and immune checkpoint inhibitors, and cancer vaccines. All these approaches employ different mechanisms to trigger an immune response against cancer cells, and their effectiveness and safety have been described to be different in children (3). For instance, CAR-T cell therapy has successfully treated relapsed or refractory ALL, which is among the most prevalent pediatric cancers (4). This technique involves the modification of an individual's T cells so that they can detect and kill cancerous cells the first-in-human CAR-T cell trials show promising outcomes (5).

The opportunities of immunotherapy for pediatric hematologic malignancies also have limitations, especially about toxicity. Immune-related adverse reactions may be classified into grades 1-5 and are relatively common, with immunotherapy-associated toxicity ranging from mild to life-threatening. These toxicities are more worrisome in children as their immune system and developmental phenotype are distinct from adults, requiring additional strategies to identify and handle side effects (6). Over time, scientists have provided grading systems and management techniques for these toxicities so that immunotherapy has positive safety aspects that will favor the children (7).

Immunotherapy, in particular CAR-T cell therapy, is one of the most successful in children with hematologic cancers, particularly B-cell ALL. CAR T-cell therapy is a type of immunotherapy because it is designed to combat cancer cells wholly selectively. In contrast, engineered T cells are designed to identify certain antigens in cancer cells. However, some concerns still persist, primarily the cytokine release syndrome (CRS) and neurotoxicity, both of which are fatal side effects that must be closely managed (4, 8). For example, other researchers have established that first-line B-ALL pediatric patients receiving Carb-T therapy to treat the disease had significantly high remission rates, severe CRS remained a major issue and required effective clinical management (9).

Another type of immunotherapy is monoclonal antibodies in childhood hematologic cancers like blinatumomab and inotuzumab. These antibodies work on definite markers on the cancer cells so that the immune system can more easily identify and kill malignant cells. The clinical use of blinatumomab and inotuzumab among children with relapsed or refractory B-ALL has been clinically effective, with their outcomes reflecting increased remission rates and survival (7). Compared to CAR-T therapy, monoclonal antibodies do not involve manipulating a patient's cells thus, the treatment could be less rigid and probably faster to perform (10).

Other agents, particularly immune checkpoint inhibitors, for example, pembrolizumab, have also been tried in pediatric hematologic malignancies. Checkpoint inhibitors have proved to be very successful in adult cancers, where they are able to block proteins that suppress immune responses, but their success in cancer treatment for children has been limited, and more research needs to be done. Literature shows that checkpoint inhibitors may be useful in pediatric patients with specific relapsed cancers, but the areas of applicability in this population are somewhat less broad compared with other immunotherapies (8, 11). However, survival trials are still conducted to understand how checkpoint inhibitors can be used with other immunotherapies for children's benefit (9).

The optimization of combination immunotherapy treatments is extremely supportive for childhood hematologic cancers. Integrating CAR-T cells, monoclonal antibodies, and checkpoint inhibitors is proposed to improve immunotherapy activity against cancer cells and eliminate drawbacks that are inherent to each of the mentioned methods when applied as monotherapy (12). In other combination therapy trials published within the last year, overall response rates have been higher, and toxicity profiles have been more easily controlled in pediatric patients. For example, CAR-T cell cooperates with a checkpoint inhibitor and has been synergistic in preclinical models of leukemia (13).

As with most therapeutic strategies, there are still issues with fine-tuning the methods of delivering immunotherapy and dealing with the specifics of the pediatric population. Whether immunotherapy is effective and safe has something to do with the type of cancer and its stage, and also the level of immune system in children and possible side effects of late effects (3,14). The latency of toxicities and issues regarding quality of life in these survivors remain a subject of future studies to address important aspects of children's health and well-being after cancer treatment (1). For example,

immune-related toxicities, such as growth, neurodevelopment, and organ toxicities, remain crucial challenges that require long-term follow-up (15).
Therefore, in response to questions of efficacy and safety, immunotherapy is sometimes not affordable to many individuals in developing countries or countries with an average income. Therefore, CAR-T cells are costly to develop and maintain and are only available to patients who could most benefit from them. Current approaches to immunotherapy remain expensive, and there is inadequate access to optimal treatment worldwide, especially for children (5, 10).

**Objective:** The goal of this work is to assess the outcomes of immunotherapy for children with hematologic malignancies and compare therapeutic outcomes, immune reactions, and risks. By evaluating available immunotherapy methods, the study will seek to advance knowledge on immunotherapeutic approaches with better prognoses, few side effects, and improved quality of life for youngsters.

## MATERIALS AND METHODS:

**Study Design:** This investigation is a real-world case-control investigation of children with hematologic malignancies who were administered immunotherapy.

**Study setting:** The data were obtained from several oncology centers associated with different offices for pediatric cancer treatment in Pakistan and China.

**Duration of the study:** The data is based on treatments given and follow-up data from January 2018 to December 2023, a five-year follow-up period.

### Inclusion Criteria:

Children in this study are those who have hematologic cancer, that is, cancer of the blood, aged 0-18 years, and have been treated with immunotherapy. Patients must have had at least one full cycle of immunotherapy.

### Exclusion Criteria:

These receptors exclude patients who received immunotherapy in combination with other experimental therapies, those who received immunotherapy before the considered period, and those who were not followed up completely.

### Methods:

The research design of choice in this study was the retrospective cohort study: the researchers reviewed patient files to determine immunotherapy outcomes in children with hematologic cancers. Outcomes embraced clinical parameters, such as disease relapse, immune system activity, and side effects. Laboratory results, imaging, and immune status data were obtained from clinical charts and confirmed through medical record review. The immunotherapy types studied were CAR T-cell therapy, monoclonal antibodies, and immune checkpoint inhibitors.
Most of the patient data collected were done using validated surrogates, like the remission status and progression-free survival rate. AEs were classified by severity based on the NCI-CTCAE version 4. Descriptive statistics were employed on the statistical software to compare baseline characteristics, treatment outcomes, and toxicity profiles in various therapies. Conventional criterion of $p < 0.05$ was used to test for statistical significance and logistic regression analysis to adjust for potential confounding factors influencing treatment response.

## RESULTS:

In the study, a total of 150 children with malignancies of the hematological system who underwent immunotherapy, including CAR T-cell therapy, monoclonal antibodies, and immune checkpoint inhibitors, were included in the analysis. Seven were children, 17 were adolescents with a mean age of 11.6 years (SD±3.6), and 12 were adolescents. Leukemia in the majority, particularly B-Cell Acute

Lymphoblastic leukemia, the center was 70% while Lymphoma was 25%, and the rest of the 5% of patients came under other hematologic malignancies.

**Treatment Efficacy**

The treatment outcome was defined by the remission rates, progression-free survival, and overall survival at the time point of the study endpoint. CAR T-cell therapy was the most effective treatment, reporting an 85% remission rate monoclonal antibody therapy had a 70% remission rate, and immune checkpoint inhibitors had a 60% remission rate. Median PFS varied by treatment type: CAR T-cell therapy had a better PFS of 24 months compared to monoclonal antibodies of 18 months and checkpoint inhibitors at 15 months. OS was also significantly higher among the recipients of CAR T-cell therapy.

Table 1 displays the remission rates, PFS, and OS for each immunotherapy to compare their efficacy.

**Table 1. Treatment Outcomes by Immunotherapy Type**

| Therapy Type | Remission Rate (%) | Median PFS (months) | Median OS (months) |
|---|---|---|---|
| CAR T-Cell Therapy | 85 | 24 | 30 |
| Monoclonal Antibodies | 70 | 18 | 22 |
| Checkpoint Inhibitors | 60 | 15 | 20 |

**Immune Response Markers**

Different molecular biomarkers, including cytokine levels, proportion or ratio of different subsets of T cells, and absolute numbers of lymphocytes, were measured to assess immune response. An observed rise in the count of CD4+ T-cells reveals immune activation across all types of treatment. CAR T-cell therapy was associated with a significant increase in the levels of interleukin -6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which reflected a more effective immune response but at the same time with the increased toxicity risk. On the other hand, patients treated using monoclonal antibodies had a moderate cytokine count, meaning that their immune response was being checked. Immune checkpoint inhibitors had relatively reduced the general cytokine secretion.

Table 2 describes the mean immunotherapy immune response markers average.

**Table 2. Immune Response Markers by Immunotherapy Type**

| Therapy Type | CD4/CD8 Ratio Increase (%) | IL-6 (pg/mL) | TNF-α (pg/mL) |
|---|---|---|---|
| CAR T-Cell Therapy | 65 | 350 | 280 |
| Monoclonal Antibodies | 45 | 200 | 180 |
| Checkpoint Inhibitors | 30 | 150 | 130 |

**Adverse Events**

Adverse events (AEs) were then categorized based on their Common Terminology Criteria for Adverse Events (CTCAE) versions, which were the most severe, with CRS, neurotoxicity, and hematologic toxicity. Severe CRS across all CAR T-cell therapies was reported to be highest in Grade 3 or higher in 30% of patients, in contrast to 15% of patients treated with monoclonal antibodies. CAR T-cell therapy treatment-related neurotoxic effects involving confusion and seizures were experienced by 20% of the patients and 10% of patients who received monoclonal antibodies. The common hematologic toxicities reported with all groups of agents were anemia and neutropenia, mild to moderate anemia, which were observed with immune checkpoint inhibitors in 40% of cases.

Table 3 details other adverse events and shows common adverse events per treatment by intensity.

**Table 3. Adverse Events by Immunotherapy Type**

| Therapy Type | Severe CRS (%) | Neurotoxicity (%) | Hematologic toxicity (%) |
|---|---|---|---|
| CAR T-Cell Therapy | 30 | 20 | 50 |
| Monoclonal Antibodies | 15 | 10 | 45 |
| Checkpoint Inhibitors | 5 | 5 | 40 |

These results suggest that, CAR T-cell therapy is the most effective treatment in terms of survival rate but is associated with the highest grade of toxicity. Introducing, there is moderate effectiveness but moderate toxicity in Mono-clonal antibody system while somewhat less effectiveness but lesser toxicity in Check point inhibitors particularly in pediatric hematologic malignancy cases.

**Discussion:** The findings of the present research further support immunotherapy in addressing children's hematologic malignancies, especially those of leukemia and lymphoma. Immunotherapy has targeted approaches in CAR T-cell therapy, monoclonal antibodies, and immune checkpoint inhibitors to improve the immune system capacity in children with hard-to-treat, relapsed, or refractory cancer. These therapies, though, have their own side efficacy factors and side effects that require utmost attention, particularly when used with children.

CAR T-cell therapy was found to be the most effective of the treatments, with an overall remission rate of 85 % and a median PFS of 24 months. These results are similar to findings from other works that compared CAR T-cell therapy on B-cell ALL, a common type of blood cancer in children (1). Technically, CAR T-cells are built to search for certain antigens in the cancer cells and destroy cancer cells directly. But despite this powerful concept, there are certain complications, such as cytokine release syndrome (CRS), neurotoxicity, and hematologic toxicity. The high rate of CRS noted in this study at 30%, with 20% of the patients experiencing severe cases of CRS, is in sync with previous studies noting that immune-related toxicities should be well managed (2). These toxicities are believed to result from the particularly vigorous immune activation induced by CAR T-cells that results in systemic inflammatory responses that, while efficacious against cancer, are also detrimental to the patient (2, 4).

Monoclonal antibody therapy was only moderately effective – 70% of patients experienced remission, the median PFS was 18 months – and was distinguished by lower severity of severe adverse effects. This therapy operation can be explained by the fact that it attaches to particular antigens at the surface of cancer cells so that the immune system has an indication that these cells have to be destroyed. The preserved CRS and neurotoxicity profile in monoclonal antibodies compared to CAR T-cell therapy reinforces the notion that it may be safer for some patients, especially young children or patients with complications that may not take severe systemic immune reactions well. These results indicate that monoclonal antibodies, which have higher efficacy than standard therapies but lower rates of serious side effects compared to CAR T-cell therapy, could be a middle ground for clinicians when caring for patients at risk of severe toxicities (3, 6).

Checkpoint inhibitors had a remission rate of 60%, a median PFS of 15 months, and comparatively lower efficacy in pediatric hematologic cancers and other hematologic malignancies. These drugs target molecules that dampen the immune response against the cancer cells and thus restore the activity of the immune response. Checkpoint inhibitors are commonly administered to adults with oncology and have demonstrated effectiveness in diverse sorts of resists used in solid tumors however, an efficacious outcome is limited in pediatric hematologic malignancies (8). The on-target toxicities with checkpoint inhibitors, like mild to moderate hematologic toxicity, were less severe than what we have seen with CAR T cell therapy, suggesting that this therapy can be relatively safe for some children, although it may not be as effective as CAR T cell therapy. This is in line with a similar finding suggesting that although checkpoint inhibitors are transformative in some cancers, the outcomes in hematologic malignancies, especially in children, are relatively better (10, 13).

The differences in immune responses documented with the treatments also point to the interplays of therapeutic mechanisms and the immune system of pediatric patients. A powerful immune activation

that stemmed from CAR T-cell therapy was illustrated after cytokine levels such as Interleukin-6 and Tumor Necrosis Factor-alpha increased sharply. These high cytokine levels are associated with both response to treatment and toxicity, including CRS and neurotoxicity (2, 4). By comparison, tutors brought into play monoclonal antibodies that cause moderate elevations in cytokines, indicating that the immune response of these drugs is less harmful and ought to be effective in preventing serious side effects (5). Checkpoint inhibitors produced the lowest level of cytokine response of all the therapies that were considered, which can be attributed to the fact that while immune-related adverse events are less common with these treatments, the same is true for the therapeutic efficacy of the treatments in hematologic cancers.

The variations concerning side effects are important in developing therapeutic strategies to meet the individual needs of a patient, especially children, where the therapeutic duration counts a lot. For instance, CAR T-cell therapy has been associated with neurotoxicity in 20% of patients, and this raises the question of whether children with still-developing brains can have similar effects that cause lasting toxicities (4). Compared with polyclonal antibodies, monoclonal antibodies that observe a better neurotoxic profile may be used where patients have higher risk of adverse neurological events. Further, the rate of severe CRS is less with monoclonal antibodies and checkpoint inhibitors, suggesting that these treatments could be more appropriate for patients with comorbidities that would make them more prone to CRS. These observations supplement a personalized approach to patient management in which treatment is guided by the patient's risk, cancer type, and the presence of comorbidities that may increase the toxicity of the planned treatment (7, 9).

However, several limitations of this study should be noted for the reader: A relatively small number of participants, which means that the results of the study are not ideal to represent the Puerto Rican population. In addition, more long-fill-up data were not obtained from all patients, and questions remain about the sustainability of remission and potential late effects, particularly neurocognitive functioning in these young survivors (11, 12). Follow-up investigations should use more centers and more patients to confirm these observations and to identify further biomarkers to further increase the accuracy of treatment response and side effect predictions. Furthermore, interacting supportive care measures include pre-treatment with ‘anti-inflammatory’ drugs that could reduce some of the severe toxicities without dampening the therapeutic effects of CAR T cell therapy (1, 15).

Finally, immunotherapy presents diverse, though not identical, therapeutic approaches for children with hematologic cancer. This therapy has the best outcome in terms of response to treatment, but it has potentially severe complications such as CRS and neurotoxicity that are demanding for both screening and treatment. Monoclonal antibodies show a favorable risk-benefit ratio, while checkpoint inhibitors are safer even though the latter may have modest benefit in pediatric hematologic malignancies. When clinicians understand these precise descriptions of each therapy, choices can be made based on the best interest of each child, depending on the chance of success and the costs of failure. Subsequent studies for identifying happy predictors and exploring more consequences will be crucial while defining immunotherapy in pediatric oncology.

## CONCLUSION

Immunotherapy can be promising in pediatric hematologic cancers, and this research proves that CAR T-cell therapy has the highest overall remission rate but, at the same time, comes with high-risk factors such as CRS and neurotoxicity. We found monoclonal antibody therapy to be safer but with moderate efficacy as opposed to checkpoint inhibitors, which provided the least side effects, although less effective. They corroborate a message that has been presented across the immunotherapy landscape consistently: that of individualizing treatment according to the patient's risk factors and overall clinical situation to provide benefits and avoid toxicity. Moreover, the significance of further exploration into predictive biomarkers and late outcomes in order to fine-tune the approaches is outlined. Finally, immunotherapy shows potential for enhanced treatment approaches in pediatric cancers but requires close management and development of a therapeutic intent for each child in order to minimize adverse effects that may follow both in the short and long term.

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