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Mini Review

Precision Immunotherapy for Pediatric Malignancies: From Molecular Profiling to Clinical Implementation

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Abstract

Introduction: Primary Immune Deficiencies (PID) of rare, under-determined diseases particularly in sub-Saharan Africa. Our aim was to share the results of the follow-up of these patients.

Patients and Methods: We conducted a descriptive and analytical cross-sectional study at the Albert Royer National Children's Hospital in Dakar, in collaboration with other pediatric departments and the Immunology laboratory of the National Blood Transfusion Center. We included all patients received with suspected PID, from 2014 to 2021, after ruling out HIV infection. The diagnostic criteria were the recommendations of the Moroccan Society of Immunology. We did not include patients with incomplete data. A complete blood count was performed in all patients. Further explorations were carried out depending on the orientation. The data was analyzed with Excel 10.

Results: Out of 32 patients registered, 16 were included in a follow-up consultation (50%). The sex ratio was 0.6 and the mean age at diagnosis was 51.1 months. Inbreeding was observed in half of the patients (8/16). The warning signs were mainly infectious (11/16). The other symptoms were dermatological, such as eczema and warts (3/16), but also neurological, type ataxia (3/16). Anemia was observed in 12/16 children, lymphopenia in 4/16 children. Protein electrophoresis was performed in 10/16 children, immunoglobulin weight determination in 4/16 children and lymphocyte immunophenotyping in 10/16 patients. The main PIDs diagnosed were congenital neutropenia (3/16), severe combined immune deficiencies or SCID (3/16), telangiectasia ataxia (3/16), hypogammaglobulinemia (2/16), verruciform epidermodysplasia (2/16), Wiskott-Aldrich syndrome (1/16), chronic septic granulomatosis (1/16), Evans syndrome (1/16). The course was marked by relapses-remissions in 6/16 patients and discontinuation of follow-up in (5/16 patients). Bronchiectasis was observed in 2 patients, with secondary bacterial and fungal infections and digital hypocratism. 100% mortality was observed in carriers of SCID and Telangiectasia ataxia.

Conclusion: PIDs are suspected based on atypical clinical signs. Confirmation is difficult in low income countries. The development is marked by a risk of complications or death, hence the need to strengthen clinical-biological collaboration.

Keywords: *Primary Immune Deficiencies; Sub-Saharan Africa*

Abbreviations

ADC: Antibody-Drug Conjugate; AI: Artificial Intelligence; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; B-ALL: B-cell Acute Lymphoblastic Leukemia; CAR: Chimeric Antigen Receptor; CLEC12A: C-type Lectin Domain Family 12 Member A; DIPG: Diffuse Intrinsic Pontine Glioma; EBRT: External Beam Radiotherapy; GD2: Disialoganglioside 2; HLH-LS: Hemophagocytic Lymphohistiocytosis-Like Syndrome; NTRK: Neurotrophic Tyrosine Kinase; PD-1: Programmed Death-1; RNA-seq: RNA Sequencing; TIL: Tumor-Infiltrating Lymphocyte; TMB: Tumor Mutational Burden; TP53: Tumor Protein 53; TRK: Tropomyosin Receptor Kinase; WES: Whole-Exome Sequencing; WHO: World Health Organization

Introduction

Pediatric cancers remain a leading cause of disease-related death in children in developed countries, accounting for approximately 15% of global childhood mortality. Yet, fewer than 10% of immunotherapy clinical trials specifically target pediatric populations. In hematologic malignancies, strategies such as CD22-targeted CAR T-cell therapies have demonstrated reduced off-target toxicity compared to conventional treatments; however, immune-related complications still occur in up to 15% of pediatric recipients [1]. Precision immunotherapy-the use of molecular profiling to tailor immune-based therapies-has emerged as a transformative approach for these malignancies, particularly in neuro-oncology, where tumor-specific antigens like GD2 in neuroblastoma are being leveraged to enhance therapeutic precision. Despite this progress, translational challenges persist, including the misapplication of adult-derived biomarkers to pediatric tumors, which often exhibit distinct mutational profiles and immune microenvironments [2]. This editorial evaluates the integration of genomic insights into immunotherapy development for childhood cancers, addressing critical barriers and age-specific biomarker discovery, while advocating for global collaboration to accelerate clinical implementation.

Molecular profiling: Unlocking tumor heterogeneity

Molecular profiling has revolutionized pediatric oncology by decoding the genomic landscapes of childhood malignancies. Techniques such as whole-exome sequencing (WES) and RNA sequencing (RNA-seq) have identified actionable alterations in approximately 44% of pediatric solid tumors, including ALK mutations in neuroblastoma and BRAF fusions in low-grade gliomas, as demonstrated in a pan-pediatric cohort study [3]. Recent advances in large-scale genomic initiatives have further elucidated the heterogeneity of pediatric tumors. A landmark analysis of 888 pediatric tumors identified recurrent, targetable mutations in 62% of cases, including CD19 overexpression in B-cell acute lymphoblastic leukemia (B-ALL) and TP53 variants in high-risk adrenocortical carcinoma [4]. Notably, this study revealed that RNA-seq–based fusion detection informed treatment changes for 18% of patients, enabling the use of NTRK inhibitors for infantile fibrosarcoma and RET inhibitors for medullary thyroid carcinoma.

Precision immunotherapy modalities

Recent advances in biomarker discovery have expanded the arsenal of precision immunotherapies identifying novel targets such as CLEC12A in pediatric AML and CD276 (B7-H3) in high-risk neuroblastoma**.** These findings have enabled the development of CLEC12A-directed CAR T-cell therapies and B7-H3-targeted antibody-drug conjugates, which show promise in early-phase trials for relapsed/refractory case [5]. Transformative potential of immunotherapeutic strategies tailored to molecular profiles including CAR T-cells targeting CD19 in pediatric B-cell malignancies and GD2-directed bispecific antibodies for high-risk neuroblastoma. This analysis emphasizes the role of tumor-infiltrating lymphocyte (TIL) therapy in pediatric sarcomas with mismatch repair deficiencies, where adoptive cell transfer has shown 40% objective response rates in early trial as well as oncolytic viruses engineered to express immune-stimulating cytokines as a promising modality for central nervous system tumors, particularly in diffuse intrinsic pontine glioma (DIPG) with H3K27M mutations [6].

Precision immunotherapy modalities

Despite advances in precision immunotherapy, ethical dilemmas such as incidental germline findings during tumor sequencing, complicate informed consent processes and delay therapy initiation in up to 20% of cases. Regulatory fragmentation further exacerbates disparities, with 60% of precision immunotherapy trials requiring protocol modifications for pediatric populations, prolonging approval timelines by 12 to18 months compared to adult studies. Additionally, the lack of pediatric-specific drug formulations and dosing guidelines for agents such as TRK inhibitors results in suboptimal toxicity management, particularly in children under five years of age [7].

Future directions: Collaborative solutions

Real-time collaboration on rare pediatric cancer cases across 15 countries is significantly advancing precision medicine efforts. Artificial intelligence tools are currently harmonizing multi-omics data, reducing biomarker discovery timelines by 40% in pilot programs targeting refractory neuroblastoma. Workforce training programs remain critical, as current data indicate that only 22% of pediatric oncologists feel confident interpreting immunotherapy biomarker reports, highlighting the urgent need for enhanced genomic literacy [8]. Furthermore, harmonizing regulatory frameworks across countries has been shown to reduce approval timelines for pediatric immunotherapies, ensuring faster access to life-saving treatments for children worldwide [9].

Conclusion

Molecular insights remain a critical challenge, particularly in pediatric cancers where tumor biology and immune responses differ fundamentally from those in adult malignancies. While precision immunotherapies such as CAR T-cells and GD2-targeted antibodies demonstrate transformative potential, their benefits remain concentrated in high-resource settings. It is of utmost importance to prioritize funding for pediatric-specific biomarker discovery and global access programs, ensuring that low- and middle-income countries can both participate in and benefit from the precision oncology revolution. Initiatives like the WHO's Global Initiative for Childhood Cancer must expand to include molecular profiling infrastructure, helping to democratize access to life-saving therapies for all children.

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