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Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL): Overview and Introduction to the Proceedings of the 2016 TACL Investigator Meeting

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Abstract

Despite great success in the development of curative therapies for pediatric hematologic malignancies, new approaches are needed to overcome resistance to treatment and to reduce associated side effects. The Therapeutic Advances in Childhood Leukemia and Lymphoma Consortium (TACL) is an early phase clinical trial group dedicated to developing innovative therapies for currently incurable pediatric leukemias and lymphomas (<https://tacl.chla.usc.edu/tacl/>). In November of 2016, a TACL Investigator Meeting was held, the proceedings of which appear in this edition of *Pediatric Hematology Oncology*. This introductory paper provides an overview of TACL and introduces the 5-part proceedings.

Keywords

leukemia; lymphoma; pediatric; clinical trials; molecularly targeted agents

Introduction

Despite great progress, hematologic malignancies remain a leading cause of death from childhood cancer,^{1,2} and survivors are at life-long risk of complications of treatment.³ New therapeutic approaches are needed to overcome chemotherapy resistance and reduce long-term toxicities.⁴

The Therapeutic Advances in Childhood Leukemia and Lymphoma Consortium: History, Mission and Organization

The Therapeutic Advances in Childhood Leukemia and Lymphoma Consortium (TACL) was founded in 2005 based on the identified need to increase early stage clinical testing of new therapies for children, adolescents and young adults with leukemia and lymphoma. TACL was established as, and remains, the only early phase clinical trial group focused solely on childhood hematologic malignancies. TACL's mission is to develop innovative therapies for currently incurable leukemias and lymphomas (<https://tacl.chla.usc.edu/tacl/>).

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Clinical trials for children with relapsed and refractory hematologic malignancies are challenging and resource intensive. The patient population is small and patients commonly have multiple co-morbidities and rapidly progressive disease that requires acute intervention. Consequently, such studies may entail labor intensive reporting of treatment-emergent adverse events and they are often complex, slow to complete accrual and expensive to conduct. Furthermore, pharmaceutical companies may not be motivated to fully support these trials especially when the target cancers are restricted to a pediatric population. TACL strives to overcome these challenges through its scientific and administrative expertise and organizational efficiency.

TACL began as a consortium of 8 member institutions. It has since grown and currently comprises 35 sites in the US, Canada, Australia and Israel. Member institutions must be dedicated to performing early phase studies in childhood leukemias and lymphomas and have relevant expertise, adequate resources and a track record of success in that regard. The TACL Operating Center, which is located at Children's Hospital Los Angeles, provides centralized support for contracting, budget management, regulatory affairs, clinical trials coordination, site training and monitoring, and statistical and database infrastructure. The Operating Center partners with the research and clinical care teams at TACL member institutions to ensure that studies are conducted in compliance with FDA, IRB and other applicable regulatory authorities. The TACL organizational infrastructure also includes a Steering and Prioritization Committee that provides scientific oversight and governs the consortium's overall research portfolio. A Scientific Review Committee, composed of one voting member from each full member institution (the site Principal Investigator), is responsible for review and approval of all studies.

TACL collaborates with academic institutions, pharmaceutical industry companies and other clinical trials groups. The consortium, its leadership and its member institutions work closely with the Children's Oncology Group (COG) and other leading cooperative groups. This ensures that TACL studies are coordinated and aligned with national and international pediatric clinical trial and research efforts, that they support future phase II and III clinical trials, and that they are integrated into overall innovative treatment and new agent development plans.

TACL Studies

As of June 30, 2017, TACL has conducted 19 studies since its inception, to which 217 patients have been accrued to therapeutic trials and 800 to registry studies.^{5,6,7,8,9,10,11,12,13,14,15,16,17,18,19} Collectively, TACL member sites screen between 300 to 500 patients with relapsed hematologic malignancies annually.

Unlike many pediatric solid tumors, children with relapsed and refractory hematologic malignancies are often acutely ill due to high disease burden and rapidly progressive disease. Such patients quickly become sicker unless remission is achieved. At its start, TACL co-sponsored an international symposium to build a consensus definition of dose-limiting toxicity in this population with multiple baseline co-morbidities and risks.²⁰ Treatment-associated toxicity commonly exacerbates disease-related cytopenias. Furthermore, new agents added to standard combination chemotherapy regimens may introduce agent-specific

adverse events or increase platform-associated toxicities, and novel combinations may result in novel toxicities. The effort to define and minimize expected adverse events associated with standard backbone chemotherapy regimens in this patient population is ongoing.¹⁴

As early as possible in new agent development a decision is required whether a particular agent or combination is worthy of further study. TACL established benchmark response rates for second and subsequent relapse by literature review²¹ and in a retrospective review of TACL experience.^{5,6} These response rates have been confirmed by others²² and in a follow-up TACL study of a subsequent treatment era.¹⁷

TACL has conducted a series of studies of novel agents that represent among the first, and in some cases the only, pediatric experience with these therapies. This includes trials of the microtubule inhibitor ABT-751,⁹ the locked nucleic acid survivin inhibitor EZN-3042,¹⁰ the synthetic retinoid derivative fentretinide, the FLT3 inhibitor quizartinib,¹¹ the toll-like receptor 9 agonist CpG oligodeoxynucleotide GNKG168, and the nucleoside analogue nelarabine.¹⁵

Based on bortezomib's value in other lymphoid malignancies ("paraclinical activity"), TACL completed a phase I trial of bortezomib plus vincristine, dexamethasone, pegylated asparaginase, and doxorubicin.⁷ The impressive CR rate in second and subsequent relapse⁸ was subsequently confirmed in a COG 1st relapse trial.²³

TACL has conducted a series of clinical trials of epigenetic modifying agents including single agent panobinostat, azacytidine in combination with FLAG chemotherapy and vorinostat/decitabine combined with the UKR3 induction platform and FLAG, all with strong correlative biologic studies.^{12,13,16,18}

Current studies include chemotherapy combinations with a proteasome inhibitor, epigenetic modifiers, an mTOR inhibitor and liposomal vincristine (<https://tacl.chla.usc.edu>), with multiple trials of molecularly targeted agents in development including immune checkpoint blockade, a gamma secretase inhibitor, and a small molecule tyrosine kinase inhibitor.

2016 TACL Investigator Meeting

In November of 2016, a TACL Investigator Meeting was held in Los Angeles, California. Proceedings of this two-day meeting appear in this edition of *Pediatric Hematology Oncology* (<http://www.tandfonline.com/loi/iph020>). These manuscripts are intended to summarize information presented and discussed at the Investigator Meeting, to provide updates on current TACL activities and to bring additional focus to the needs, challenges and opportunities in the area of pediatric hematologic malignancies. Due to study-specific confidentiality agreements, unpublished results of active and planned TACL trials are not included in these proceedings, which appear in 5 additional parts:

- 1. Biology of relapsed hematologic malignancies:** Drs. Izraeli and Chang co-chair a Biology Working Group that was assembled in advance of the TACL Investigator Meeting. The Group was formally approved as a standing committee at the meeting itself with the goal to further develop preclinical and translational studies designed to advance the understanding and treatment of relapsed and

refractory pediatric hematologic malignancies. The initial proposed activities of this Committee are summarized in the manuscript by Bhojwani et al.

2. **Tumor microenvironment in hematologic malignancies:** Interactions between leukemia blasts and stromal cells in the bone marrow microenvironment appear to be important and targetable mechanisms of therapy resistance. Drs. Sison, Kim and Kurre presented a mini-symposium on the role of the tumor microenvironment in hematologic malignancies, which is summarized in their manuscript in this proceedings with a focus on chemokine signaling via CXCR4, adhesion molecule signaling via integrin $\alpha 4$, and crosstalk mediated through extracellular vesicles.
3. **Checkpoint inhibition in hematologic malignancies:** The meeting included a series of talks on checkpoint inhibitors in hematologic malignancies. Current data of this class of agents is summarized in the paper by Drs. Verma, Agarwal and Davis.
4. **Relapse and response definitions:** Drs. O'Brien and Gaynon led a breakout session entitled *Relapse and Response Definitions in the Minimal Residual Disease Era*. That session and follow up meetings culminated in the manuscript by Huynh et al in which it is proposed that treatment failure for pediatric acute leukemia be redefined based on MRD and that trials include separate strata for patients with morphologic relapse vs. those with MRD recurrence or persistence.
5. **Medical supportive care in early phase studies:** Patients treated on TACL studies are at high risk for life-threatening treatment-related toxicities. In advance of the Investigator Meeting, a new Working Group on Medical Supportive Care was assembled under the co-leadership of Drs. Orgel and Auletta. This Supportive Care Committee was subsequently established as a standing committee charged to assist in the development, implementation and monitoring of enhanced supportive care guidelines designed to reduce the risks associated with early phase clinical trials in this patient population. The Committee's initial findings and proposed activities are detailed in the associated manuscript.

Summary

While leukemias and lymphomas of childhood share many characteristics with their counterpart diseases in adults, progress in the treatment of pediatric hematologic malignancies has been made primarily through clinical trials in pediatric populations. TACL, as an age-based, disease-focused, early phase clinical trials consortium, is dedicated to advancing the therapeutic pipeline for children, adolescents and young adults with leukemias and lymphomas. The TACL consortium has developed a robust portfolio of early phase clinical trials and has established a strong track record in the implementation, completion and publication of studies that have contributed to new agent development in pediatric hematologic malignancies.

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