Curr Probl Cancer 41 (2017) 194–200

Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Pediatric oncology enters an era of precision medicine

Nita L. Seibel, MD[a,*], Katherine Janeway, MD, MSc[b], Carl E. Allen, MD, PhD[c,d], Susan N. Chi, MD[b], Yoon-Jae Cho, MD[e,f], Julia L. Glade Bender, MD[g], AeRang Kim, MD, PhD[h], Theodore W. Laetsch, MD[i,j], Meredith S. Irwin, MD[k], Naoko Takebe, MD. PhD[l], James V. Tricoli, PhD[m], Donald Williams Parsons, MD, PhD[n,o]

ARTICLE INFO

Keywords:
Genomic profiling
Adolescent and young adult cancer
Pediatric tumors
Whole-exome sequencing

ABSTRACT

With the use of high-throughput molecular profiling technologies, precision medicine trials are ongoing for adults with cancer. Similarly, there is an interest in how these techniques can be applied to tumors in children and adolescents to expand our understanding of the biology of pediatric cancers and evaluate the clinical implications of genomic testing for these

[a] *Division of Cancer Treatment and Diagnosis, Clinical Investigations Branch, National Cancer Institute, Rockville, Maryland*
[b] *Department of Pediatric Oncology, Dana-Farber/Boston Children's Cancer Center and Blood Disorder Center, Boston, Massachusetts*
[c] *Texas Children's Cancer Center, Texas Children's Hospital, Houston, Texas*
[d] *Division of Pediatric Hematology-Oncology, Baylor College of Medicine, Houston, Texas*
[e] *Department of Pediatrics, Oregon Health & Science University, Papé Family Research Institute, Portland, Oregon*
[f] *Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon*
[g] *Department of Pediatrics, Columbia University, New York, New York*
[h] *Division of Oncology, Children's National Health System, Washington, DC*
[i] *Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas*
[j] *Pauline Allen Gill Center for Cancer and Blood Disorders, Children's Health, Dallas, Texas*
[k] *Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada*
[l] *Division of Cancer Treatment and Diagnosis, Investigational Drug Branch, National Cancer Institute, Rockville, Maryland*
[m] *Division of Cancer Treatment and Diagnosis, Cancer Diagnosis Program, National Cancer Institute, Rockville, Maryland*
[n] *Department of Pediatrics, Baylor College of Medicine, Houston, Texas*
[o] *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas*
**Correspondence to: Nita L. Seibel, MD, National Institute of Health, National Cancer Institute, 9609 Medical Center Dr 5W350, MSC9757 Bethesda, MD.*
E-mail address: Seibelnl@mail.nih.gov (N.L. Seibel).

http://dx.doi.org/10.1016/j.currproblcancer.2017.01.002
0147-0272/Published by Elsevier Inc.

RNA sequencing
Next-generation sequencing

patients. This article reviews the early studies in pediatric oncology showing the feasibility of this approach, describe the future plans to evaluate the clinical implications in a multicenter clinical trial and identify the challenges of applying genomics in this patient population.

Published by Elsevier Inc.

Introduction

Improvements in outcomes for children and adolescents with cancer have been seen over the past 4 decades. Currently, 8 of 10 children diagnosed with cancer will be alive 5 years from the time of diagnosis and most of them much longer.[1] Nevertheless, challenges remain in trying to improve the outcomes for all children diagnosed with cancer and particularly in high-risk patients. Precision medicine trials are ongoing in a variety of forms for adults with cancer (as detailed in this issue in articles about National Cancer Institute-Molecular Analysis for Therapy Choice [NCI-MATCH], MPACT, LungMAP, and Alchemist). Similar approaches are being applied to children and adolescents with cancer and are currently under investigation in pediatric oncology. The purpose of this article is to describe how precision medicine is being applied to pediatric oncology and the unique challenges associated with these efforts.

Pilot studies of precision medicine in pediatric oncology

Although biomarker-driven targeted therapies are not new to pediatric oncology, combining this with individualized genomic analysis is.[2-4] Several pediatric oncology studies have explored the feasibility and use of genomics-driven precision medicine and provided the foundation for pursuing this approach. They cover different aspects of precision medicine and have different study designs, including patient population (solid tumor, central nervous system [CNS] tumors, and hematopoietic tumors; age), timing of specimen acquisition (either diagnosis or relapse or both), and inclusion of routine germline analysis. Of note, none of the published studies include prospective treatment arms as part of the study, although several studies include clinical follow-up to assess whether patients were treated according to genomics-based recommendations and evaluate subsequent outcomes.

The Baylor College of Medicine Advancing Sequencing in Childhood Cancer Care (BASIC3) study recently completed enrollment of a primary cohort of 287 newly diagnosed and previously untreated patients with CNS and non-CNS solid tumor.[5] Whole-exome sequencing (WES) was performed both on tumor samples and peripheral blood. In the report of the first 150 patients (<18 years of age) of which 121 tumors were sequenced, 33 patients (27%) were found to have somatic mutations of established or potential clinical use. An additional 24 patients (20%) were found to have mutations in consensus cancer genes that were not classified as targetable. Fewer than half of the somatic mutations identified were in genes known to be recurrently mutated in the tumor type tested. Diagnostic germline findings related to patient phenotype (either cancer or other diseases or both) were discovered in 15 (10%) of 150 cases including 13 (8.6%) with pathogenic or likely pathogenic mutations in known cancer susceptibility genes. Treatment decisions or recommendations were not part of this study.

The University of Michigan Pediatric Michigan Oncology Sequencing (PEDS-MIONCOSEQ) study is modeled after the sequencing experience in adults with cancer.[6] Although the study is ongoing, preliminary results of a cohort of pediatric and young adult participants have been reported. The study population included 102 pediatric and young adult patients (25 years of age and under) with refractory, relapsed cancer as well as newly diagnosed patients (20% of patients) with high-risk or rare cancer types. Patients with both hematopoietic malignancies and solid tumors were included. A total of 91 patients underwent genomic analyses with whole-exome sequencing of tumor and germline DNA as well as RNA sequencing of tumor. A multidisciplinary