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Current state of pediatric sarcoma biology and opportunities for future discovery: A report from the sarcoma translational research workshop

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Sarcomas are a rare subgroup of pediatric cancers comprised of a variety of bone and soft-tissue tumors. While significant advances have been made in improving outcomes of patients with localized pediatric sarcomas since the addition of systemic chemotherapy to local control many decades ago, outcomes for patients with metastatic and relapsed sarcoma remain poor with few novel therapeutics identified to date. With the advent of new technologies to study cancer genomes, transcriptomes and epigenomes, our understanding of sarcoma biology has improved tremendously in a relatively short period of time. However, much remains to be accomplished in

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this arena especially with regard to translating all of this new knowledge to the bedside. To this end, a meeting was convened in Philadelphia, PA, on April 18, 2015 sponsored by the QuadW foundation, Children's Oncology Group and CureSearch for Children's Cancer that brought together sarcoma clinicians and scientists from North America to review the current state of pediatric sarcoma biology and ongoing/planned genomics based clinical trials in an effort to identify and bridge knowledge gaps that continue to exist at present. At the conclusion of the workshop, three key objectives that would significantly further our understanding of sarcoma were identified and a proposal was put forward to develop an all-encompassing pediatric sarcoma biology protocol that would address these specific needs. This review summarizes the proceedings of the workshop.

Keywords Pediatric sarcoma, genomics, precision medicine, molecular profiling, patient derived xenografts, sarcoma biology

Introduction

Sarcomas are rare mesenchymal tumors arising from the bone or soft tissue that affect all ages but are relatively more common in the pediatric age group. Despite their rarity, they constitute significant mortality burden of about 13% of cancer related deaths in patients 0–19 years of age (1–3). Each of the sarcoma sub-types has a distinct genetic profile and phenotype with some such as osteosarcoma characterized by a highly unstable and complex genome, while others such as Ewing sarcoma characterized by a translocation between *EWSR1* gene and a variety of *ETS* partners as the single major oncogenic driver (4). Similarly, rhabdomyosarcoma can be molecularly sub-classified into fusion positive (*PAX-FOXO1* translocation) and fusion negative RMS (5). Despite the fact that the biology of individual sarcoma sub-types is vastly different, their treatment has historically been very similar including a combination of conventional chemotherapeutics, surgery and radiation. In addition, limited non-clinical prognostic markers exist for adequate risk stratification of patients to allow for therapy modifications (intensification of therapy for poor-risk groups or reduction of therapy for good-risk groups) for the majority of pediatric sarcomas. With the exception of recurrent RMS and a few rare soft tissue sarcomas, molecularly targeted therapies have not been incorporated into standard treatment at either diagnosis or recurrence and consequently therapy relies almost exclusively on cytotoxic chemotherapy.

While the current therapeutic approaches have been successful in improving outcomes of patients with localized sarcomas to 5-year event-free survival rates, of 60–70%, survival for patients with metastatic disease remains below 20–30% and those with relapsed disease is below 10–20% (2,3,6,7). In addition, pediatric patients who are cured of their disease are at a very high risk of long term morbidity and mortality due to the adverse effects of the toxic therapies to which they are exposed to at a young age. Therefore, an urgent unmet need remains to identify novel therapeutic strategies for pediatric sarcomas which can only be fulfilled by continued efforts to develop a deeper understanding of the biology of each individual subtype in the context of both the tumor itself and the host environment. As each of these individual sarcomas are extremely rare and will continue to be further molecularly sub-classified as novel genetic aberrations are discovered, it is imperative that research efforts are undertaken in a collaborative fashion to make the most impact in patient care.

A workshop, supported by the QuadW foundation, Children's Oncology Group (COG) and the CureSearch foundation, was held on April 18, 2015 bringing together basic and translational scientists as well as clinical researchers from North America to review the current state of the art of pediatric sarcoma biology as well as genomic profiling technologies with the overarching objective of identifying areas of further research opportunities that would be complementary to ongoing efforts by individual institutions and national cooperative groups such as the COG. At the end of the workshop, three potential high-impact areas of research were identified that need to be addressed at present. These include (1) establishment of better measures to identify patient prognosis and response to therapy by analysis of circulating tumor DNA; (2) analysis of a variety of germline genetic alterations such as in the gene *TP53* that may impact development and progression of sarcomas; and (3) development of novel techniques of freezing tissue samples that would allow for creation of patient derived xenografts (PDXs) in the context of standard therapy or clinical trials. Herein, we provide a brief overview of the proceedings of this workshop.

Genomic analyses of pediatric sarcomas

The spectrum of technologies to identify genetic make-up of tumors has evolved over time from conventional cytogenetics to next generation sequencing (8,9). Several large efforts to characterize the molecular landscape of sarcomas using next generation sequencing technology platforms are ongoing. While these technologies, and the techniques to interpret vast amounts of data, are being continuously refined, the meeting highlighted comprehensive genome sequencing efforts across the more common pediatric sarcomas including osteosarcoma, Ewing sarcoma and rhabdomyosarcoma. In addition to detailing the tumor biology of these sarcomas, the contribution of germline aberrations toward an increased predisposition to develop these tumors was also discussed.

Osteosarcoma—tumor genomics

Several investigators have previously published sequencing (either targeted mutation, whole genome or whole exome) results from sample sets of osteosarcoma tumors (10,11). A common theme that emerges from most of these studies is that the osteosarcoma genome is complex with a large number