Development of novel therapies for pediatric cancer: Successes and challenges

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Peter J. Houghton from Greehey Children's Cancer Research Institute and Mary-Ann Bjornsti from the University of Alabama discuss some of the key challenges in the development of therapies for pediatric cancer care

Despite pediatric cancer being a rare disease, constituting less than 1% of cancers overall, research into developing new effective and less genotoxic therapy is of critical importance. 'Significance' in terms of clinical research, for many, is determined by the number of patients afflicted with a particular cancer type. For example, in the US, there are approximately 150,000 new diagnoses for non-small cell lung cancer annually or about ten times the number of all pediatric cancers diagnosed. However, viewing pediatric cancer from the perspective of life-years saved, one can see that giving a child sixty plus years of good quality life is not only 'significant' but is actually cost-effective from the perspective of societal impact. Further, the burden on families following a cancer diagnosis for their child is enormous, both emotionally and financially. That stated, developing novel, effective new agents for the treatment of childhood cancer poses challenges. For three decades, most therapies for pediatric cancer have relied on chemotherapy, with or without external beam radiation. These treatments are toxic and genotoxic and often lead to secondary malignancies or life-threatening long-term sequelae.

The importance of understanding cancer pathogenesis

Multimodality treatment, including surgery and chemo-radiation therapy, has proven curative in about 70% of patients, yet the quality of life in survivors remains a considerable risk factor. For some childhood cancers, such as standard-risk acute lymphoblastic leukemia and nephroblastoma (a malignancy of the kidney), overall survival exceeds 90%. For other cancers, developing new effective therapies will depend on a greater understanding of the underlying genetic or epigenetic changes that drive malignant transformation and understanding the mechanism(s) by which cancers become resistant to treatments. Understanding mechanisms of malignant transformation clearly can lead to better therapeutics, imatinib being an example in chronic lymphocytic leukemia. The finding that the menin protein is essential for transforming infant mixed lineage leukemia (MLL) has led to the development of very effective inhibitors that are now in clinical development for both pediatric and adult indications. Understanding the molecular basis for childhood low-grade glioma has led to novel and much more effective treatments that appear to be far more tolerable than standard chemo-radiation. Patients with tumors characterized by the tandem duplication between KIAA1549::BRAF genes

respond to inhibitors of MEK, part of the mitogen-activated protein kinase (MAPK) signaling pathway that drives tumor cell proliferation. In patients where the tumor is driven by activating point mutations in BRAF, BRAF inhibitors combined with MEK inhibitors have led to long-term disease control, with objective response rates four times greater than traditional chemotherapy. As low-grade glioma represents the majority of pediatric brain tumors, this result represents a 'significant' breakthrough and maybe a 'game-changer' for these patients as these treatments appear less toxic than chemotherapy and will probably have less genotoxic activity.

While the molecular therapy of low-grade glioma serves as a model for the successful translation of basic research, many challenges remain. Activating mutations in BRAF also occur in gangliogliomas, epithelioid glioblastomas, glioblastomas diffuse astrocytomas, and pleomorphic xanthoastrocytomas. Thus, therapy targeted at the MAPK pathway may potentially have a broader impact than just low-grade glioma. Preclinical studies, however, suggest that in higher-grade glioma models such as diffuse anaplastic astrocytoma or glioblastoma, resistance to combined MEK/BRAF inhibitors may develop quite rapidly. Building effective therapies upon the MAPK inhibitors that prevent the development of drug resistance remains a challenge, as does developing any effective treatment for diffuse intrinsic pontine glioma (DIPG), a malignancy driven by a single mutation (K27M) in histone H3.

Drug development for childhood cancers

The slow pace of introducing effective new therapeutics to treat children with cancer must be frustrating for any parent with a child thus afflicted, or indeed for patient-care teams. There are many reasons that development is slow. For example, the incidence of a particular cancer diagnosis may be low, maybe 200 – 300 patients per year in the US, so running clinical trials is a challenge as not many drugs/agents can be tested. Many pediatric cancers arise due to gene fusions that encode proteins that are considered undruggable, such as the EWS-FLI1 translocation in Ewing sarcoma or PAX3-FOXO1 fusion in alveolar rhabdomyosarcoma. Although basic research in academia has focused on such targets, Pharma has largely avoided investing in difficult targets, particularly where the 'market' for an effective drug is essentially non-existent. Yet, in some respects, the slow rate of drug development resides also in how we conduct clinical trials by cooperative groups in the US. Taking, as an example, rhabdomyosarcoma, a tumor of soft tissue that has skeletal muscle elements, multiple clinical trials over the past 40 years have not improved outcomes for patients with advanced or metastatic disease; 25% of patients with high-risk disease progress during year one on therapy, and by 24 months, 80% experience some disease progression. Yet these patients can be identified at diagnosis as having poor outcomes but are treated with multimodality therapies where failure, and ultimately death, is 80%.

Perhaps our approach to identifying effective new agents and furthering their development path to the clinic needs some revision. A promising new agent in preclinical testing will advance to phase 2 for testing against previously treated patients resistant to standard-of-care drugs. Clinical trials have shown these patients are poor indicators of

how a patient at diagnosis would respond. Yet, new agents are not used upfront as even patients who fail current treatments may benefit from standard of care. The overall five-year event-free survival for all pediatric patients is greater than 80%, indicating that even non-curative therapy may benefit. Perhaps it is time to revisit how we introduce new agents or novel therapies earlier in disease progression for high-risk patients. [(1)] For diseases with truly dismal outcomes, such as DIPG, novel treatments are being used at diagnosis, as current therapies are essentially ineffective. Perhaps a less conservative approach to drug development must be applied to cancers where current therapy has some benefit, but where conventional drug development has not improved outcomes for the past several decades. Introducing novel therapies identified in preclinical testing, such as immunotherapy or antibody-drug conjugates (ADCs), earlier in the course of disease progression may be one approach to breaking the rather stagnant approach to improving outcomes for high-risk pediatric patients.

References

1. Houghton PJ, Kurmasheva RT. Challenges and Opportunities for Childhood Cancer Drug Development. Pharmacol Rev. 2019;71(4):671-697.

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Greehey Children's Cancer Research Institute
The Department of Molecular Medicine provides an interdisciplinary program of study in the areas of cancer and aging and their prevention.