Progress by international collaboration for pediatric renal tumors by HARMONIsation and Collaboration: the HARMONICA initiative

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Introduction

Since the initial attempts to treat children with renal cancer over 50 years ago, outcome for children with renal cancer has generally become promising. While the first endeavors mainly included surgical treatment, in the early 60s radiotherapy and chemotherapy were introduced, leading to cure of patients, including some with metastatic disease. (1) Since then, overall survival rates for the most common type of renal tumors in childhood (nephroblastoma or Wilms tumor) have improved to more than 90 percent. These excellent treatment outcomes are similar in the 2 largest clinical trial groups (the Children's Oncology Group Renal Tumor Committee (COG-RTC; former National Wilms Tumor Study Group (NTWSG)), and the International Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG). Despite the difference in upfront treatment choice (primary surgery when feasible (COG-RTC) or preoperative chemotherapy (SIOP-RTSG)) both groups have optimized the stratification of patients in their trials by modifying the intensity of treatment according to individual risk factors, in order to improve outcome for high-risk renal tumor types, but also to reduce early and late toxicity in lower and intermediate risk tumors as much as possible. (2-4)

This improvement in risk stratification has resulted in better outcomes and less cancer related toxicity. However, for remaining small subgroups of pediatric renal tumor patients, with very poor outcomes, further understanding of the underlying biology, in correlation with clinic-pathological characteristics, is an unmet need. Further, standard multidisciplinary treatment (surgery, radiotherapy, chemotherapy) can be challenging to access and/or deliver in some low and middle income countries (LMIC). The power inherent in international collaboration to address these challenges was a driving principle that supported the creation of the HARMONICA (HARMONIzation and COllaboration) initiative in 2015, when we established an organized collaborative structure for transatlantic experts from COG-RTC and SIOP-RTSG. The mandate of HARMONICA is to identify specific challenges for pediatric renal tumor subsets in order to meet the aims of our global approach to cure every child with a renal tumor with limited toxicity.

The HARMONICA group meets at least once a month by videoconferences, and as much as possible also face to face, at least once or twice a year, during existing pediatric cancer conferences. In addition, several transatlantic HARMONICA expert subgroups are collaborating on specific topics. All work is currently done by a tremendous engagement of many enthusiastic members of both study groups. Despite the fact of obvious advantages, HARMONICA is still lacking funding and needs to optimize their structure as a legal entity. Notwithstanding such limitations, in this special issue of PBC, we present the achievements, the challenges, and the future perspectives, identified by these expert groups.

Achievements through international collaboration in pediatric renal tumors

Over the past decades, a focus on collaboration, rather than on differences in approach, has opened the door for SIOP-RTSG and COG-RTC to make translational steps on a global level towards better care. An article of Giulio D'Angio, one of the pioneers in Pediatric Oncology, addressed the question of pre- or postoperative therapy for Wilms' tumor in 2008, when he wrote: "SIOP participants, their North American colleagues, and other investigators have conducted this debate in a thoroughly collegial manner. Members of any study are welcome to attend meetings of other groups, where advice and data are willingly interchanged. The children have been the beneficiaries, as they should be." (5) . It was again Giulio D'Angio, who stated that ''the investigators have achieved what political and religious leaders have not accomplished so far", (6) after the very first joint publication, in which data sets of children with renal tumors up to the age of 6 months were merged illustrating the benefits of such a collaborative endeavor. (7) These early efforts led to a global ''surgery first"" consensus for such young infants. A collaborative consensus guideline for the management of adult Wilms tumors was developed as well, (8) as was a meta-analysis on the potential role of high dose chemotherapy with stem cell rescue for relapse Wilms tumor. (9) Targeting the IGF pathways was summarized as a collaborate effort resulting from the SIOP/COG ENCCA conference. (10) Intergroup mentoring of young investigators in the field of molecular genetics of WT and CCSK revealed the molecular landscape of DAWT, FHWT and CCSK through the TARGET initiative. (11-14)

More recently, during the HARMONICA era, coordinated parallel manuscript/research efforts from COG/SIOP have focused on imaging surveillance, (15, 16) stage 1 DAWT (17, 18) and WAGR and WT. (19, 20) Collaborative reviews on unmet needs in WT, (21) addressing international progress in WT, (3) WT phase 1 and 2 studies, (22) congenital mesoblastic nephroma, (23) renal cell carcinoma (24) Wilms tumor broadly, (25)) and more recently a comprehensive position paper on oncofertility issues pertinent to pediatric renal cancer (26) have been finalized.

Since the onset of HARMONICA, clinical outputs from such international collaboration have produced practice changes in both cooperative groups. The COG has adopted post-chemotherapy histology in patients with bilateral Wilms tumor who undergo delayed nephrectomy, using post-chemotherapy histologic risk criteria defined by SIOP. The SIOP has adopted the COG approach to defining lung metastases and select abdominal radiotherapy dosing guidelines for CCSK. Both groups have adopted a harmonized definition to relapse Wilms risk classification, based on upfront treatment intensity and histologic risk criteria. Such advances only touch the surface of what is possible through data sharing and meaningful open communication and dialogue.

Challenging knowledge gaps

For future progress, HARMONICA envisages to collaborate through multidisciplinary activities on the levels of discipline groups and panels. This organized collaborative structure for transatlantic experts from COG-RTC and SIOP-RTSG aims to optimize progress for children with renal tumors. Most important is to attract relevant stakeholders including policy makers, parents and long-term survivors but also funding agencies. This will allow attainment of knowledge and achievement of goals by involving, recruiting, and exchanging talented students and young investigators, and by including LMICs as partners, for developing curative strategies. All this will further enhance access of care for each child with renal cancer worldwide, which is also a goal of SIOP and WHO. In effort to expedite such collaboration, we have identified areas of research that could benefit from international dialogue and collaboration and are the subject of a series of the 10 manuscripts that follow, each first authored by young investigators that bring new ideas and fresh perspective into the field of pediatric renal cancer. Briefly, the major themes explored in each of these manuscripts is described below.

Epidemiological challenges, addressed by Libes et al, are not limited to distinct database processes and definitions between the cooperative groups and within the various LIMIC countries. Opportunities from improved diagnostics, biobanking and integration of molecular testing are discussed, as is the advantages of improved central review of pathology and imaging. A global registration and data sharing initiative concept is introduced.

Understanding the challenging definitions of nephrogenic rests pathologically and radiographically, as well as nephroblastomatosis are critical first steps before data sharing or comparative clinical trial data can be advanced, is discussed by Fialkowski et al. Somewhat related, Welter et al. address the pathophysiology of bilateral and multifocal Wilms tumor and review renal tumor epigenetic and genetic predisposition syndromes. Correlating biology with clinical parameters including chemoresponse and survival outcomes including organ function are likely to benefit from such ongoing international collaboration.

The field of tumor biomarkers, tumor heterogeneity, and the application of liquid biopsy is tackled by Walz et al., wherein targeted pre-clinical research and data sharing is highlighted as future opportunities to ultimately inform treatment strategies and impact patient outcomes. Hont et al. subsequently review key translational aspects of pediatric renal tumor microenvironment and considerations for potential immunotherapy.

Various similarities and controversies in renal tumor imaging between the COG and SIOP are addressed by van der Beek et al. Future innovative technologies and concepts, amenable to study optimally through intergroup collaboration, are highlighted. Anatomic considerations are further explored by Tracy et al. and a surgeon-oriented but multidisciplinary group of authors wherein they share consensus opinions regarding the limitations of partial nephrectomy and controversies surrounding the approach to intravascular tumor extension. Technical advances in the surgical management of Wilms tumor, focusing on future directions and controversy of minimally invasive surgery, image guided surgery and fluorescence-guided surgery, and optimization of the surgical approach to lymph nodes are discussed by Romao et al. Analogously, McAleer et al. review the consensus, controversies and future directions of radiotherapy for Wilms tumor, noting knowledge gaps and opportunities for future research in the areas of advanced radiotherapy technologies including IMRT and proton beam therapy, the impact of molecular markers on RT indications, mitigation of reduced fertility through modulated radiation approaches, and promotion of radiotherapy late effects research, much of which can be more optimally advanced through international efforts.

In the final manuscript, Ortiz et al. address advances in the clinical management of high-risk Wilms tumor. The shifting definition of 'high risk' and which patients that includes is addressed, accounting for shifting outcomes and limited resources that can impact outcomes greatly. Advancements in laboratory (biology, tumor model, drug screening) and early phase clinical trials focusing on patients with pediatric renal tumors is emphasized.

It is acknowledged that a key limitation of intergroup collaboration is the discrepant upfront approach to patient management. The preferred approach of randomized trials to address key advances is a challenge to pursue via intergroup collaboration because of such global differences in upfront treatment approaches. Regulatory and pharmaceutical industry challenges are also present, especially for new agent trials, when international multi-group smaller (patient number) trials are being considered. Strategies may be available, however, to overcome these potential barriers. For example, the COG RTC and SIOP RTSG also convened to propose a similar chemotherapeutic backbone for children with rhabdoid tumor, upon which different biologics would be added by the different cooperative groups, obviating the need for complex new drug trials combining cooperative groups, but enabling comparison of outcome data. Through sharing of ideas, data, and research on an international level, efforts like HARMONICA hold promise to move the pediatric renal tumor field in the direction that benefits all children with renal tumors globally. Nevertheless, access to such high-tech innovations and molecular driven personalized treatment developments including advanced and novel surgical and radiotherapeutic techniques need to be enhanced in Low- and Middle-Income Countries (LMICs).

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