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Review article

Indian Pediatric Oncology Group (InPOG) – Collaborative research in India comes of age

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ABSTRACT

Treatment of children with cancer on clinical trials, often in the context of national and international co-operative groups, is one of the cornerstones of pediatric oncology treatment and has been shown to improve outcomes of children with cancer. While enrolling children with cancer in prospective multi-centre trials has become the norm in high-income countries, it has remained an exception in low and middle-income countries until recently. In this article, we briefly review the global landscape of pediatric oncology co-operative groups and then discuss the Indian scenario including more recent developments of the formation and galvanization of the Indian Pediatric Oncology Group (InPOG). The mission of InPOG is to improve the outcomes of children with cancer in India by collaborative research. A roadmap for the development and conduct of an InPOG study has been created and 21 disease-specific subcommittees have been formed. Multi-centre studies on Hodgkin lymphoma and acute lymphoblastic leukemia are currently recruiting and several others are under development.

Management of children with cancer offers one of the most striking examples of progress in modern medicine. In the 1950s, less than 10 percent of children with cancer were cured. Today, nearly 80 percent will survive the disease [1,2]. Many factors can be attributed for this progress: multimodality treatment, combination chemotherapy, improved drugs, risk stratification and supportive care. Underpinning all these has been the early incorporation of research and multi-centre clinical trials often in the context of national (and increasingly international) co-operative groups [3–6]. Such an approach, which is one of the cornerstones of pediatric oncology treatment, has been shown to improve outcomes of children with cancer [6–8] and is the accepted form of delivering treatment in the 21st century [4,9].

Collaboration in treating children with cancer is a necessity as it is a relatively rare disease. This allows for pooling of data, comparison of results, and ultimately, improved outcomes. By systematically testing novel agents and treatment combinations/schedules in comparison with alternate protocols (often ina randomized fashion), the studies from cooperative groups have helped determine the most effective agent or treatment strategy which is then incorporated into successive clinical trials. Moreover, the multidisciplinary nature of these groups brings together professionals from diverse backgrounds and different expertise, hence allowing for exchange of ideas, discussion and innovation.

In this article, we briefly review the global landscape of pediatric oncology co-operative groups and then discuss the Indian scenario including more recent developments of the formation and galvanization of the Indian Pediatric Oncology Group (InPOG).

1. Evolution of global pediatric oncology co-operative groups and collaborative research

The origins of pediatric oncology co-operative groups can be traced back to 1955 with the formation of the Cancer and Leukemia Group B Cooperative Group as well as the Acute Leukemia Chemotherapy Cooperative Study Group A (forerunner of the Children's Cancer Group), both in USA [4,10]. Published in 1960, the comparison of 6-mercaptopurine versus the combination of 6-mercaptopurine and azaserine in the treatment of acute leukemia in children, is regarded as the first multi-centre co-operative clinical trial in childhood cancer [11]. Over the next two decades, other

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co-operative groups including Southwest Cancer Chemotherapy Study Group (forerunner of the Pediatric Oncology Group), National Wilms Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group were established in USA [4,10]. All these groups conducted landmark multi-centre prospective clinical trials allowing for significant advancements in the outlook of children with cancer [10]. In the year 2000, they all merged into a single cooperative group - the Children's Oncology Group (COG) in order to combine efforts, accelerate progress and share resources. With over 5000 members from 240 pediatric cancer centers located in seven countries (Australia, Canada, Mexico, Netherlands, New Zealand, Switzerland, USA) more children with cancer have been treated by COG than by any other group [4,10]. Recently COG has brought out a series of publications which serve as a five year blueprint for research within the organization [12].

Emulating the practice from USA, similar co-operative groups were formed mainly in Europe and some other high-income countries(HIC) like Japan. The earliest and most notable among these groups were the United Kingdom Children's Cancer Study Group (forerunner of the Children's Cancer and Leukaemia Group) and the various working groups in Germany for leukemias (including BFM which represented centres in Berlin, Frankfurt and Munster) and solid tumorsnow fused under the Society for Paediatric Oncology/Haematology representing Germany and Austria [13,14]. 70–90% of children with cancer in these countries are enrolled on clinical trials [13,14]. Despite formation of national co-operative groups, the rarity of several childhood cancers like medulloblastomas [15], Hodgkin lymphomas [16], neuroblastomas [17], Wilms tumour [18], liver tumours [19] and sarcomas [20,21], has necessitated collaborations in Europe (several under the umbrella of International Society of Pediatric Oncology) with clinical trials which have transcended geographical boundaries. For clinical trials on certain childhood cancers like osteosarcoma and B-cell non-Hodgkin lymphoma there have even been transatlantic collaborations between COG and European institutions [22,23].

While enrolling children with cancer in prospective multi-centre trials has become the norm in HIC, it has remained an exception in low and middle-income countries (LMIC) until recently. The clinical trials conducted by the Brazilian Pediatric Oncology Group is an example of such exception, although only a minority of children with cancer in Brazil get enrolled on their clinical trials [24]. In such a backdrop at the start of the 21st century, multi-centre, multinational collaborative efforts have sprouted in LMIC with Central America and Africa leading the way. The Asociación de Hemato-Oncología Pediátrica de Centro América(established 1998) is a consortium of seven Central American countries (Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, Panama, Dominican Republic)supported by several institutions in North America and Europe [25]. An area of focus has been the development of shared clinical protocols which now exist for most childhood cancers [25], and results based on the prospective use of some of these have been published [26–28]. Another example has been the Franco-African Childhood Cancer Group, established in 2000, which currently includes 15 countries in francophone Africa supported by institutions in France [29]. They have published prospected muti-centre studies on Burkitt lymphoma and Wilmstumour [30–32] with collaborative work ongoing on acute lymphoblastic leukemia, Hodgkin lymphoma and retinoblastoma [29]. The latest entry into these path-breaking collaborations in LMIC has been the Collaborative WilmsTumour Africa Project, an initiative by colleagues from 8 institutions in 5 countries in Sub-Saharan Africa (Cameroon, Ethiopia, Ghana, Malawi, Uganda) which are among the poorest in the world [33]. Another exciting development has been the recent collaboration in the field of pediatric and adolescent germ cell tumors between several institutes in HIC and institutes from Brazil, Egypt and India [34].

2. The history of collaborative efforts in pediatric oncology in India

Dedicated pediatric oncology units first started to appear in India in the early 1980s and were confined to major metropolitan centres. The Pediatric Hematology and Oncology (PHO) chapter of Indian Academy of Pediatrics (IAP) was established in 1987 [35]. With a focus on building capacity and quality by training, it embarked upon organizing conferences and workshops, along with initiating fellowship programs including the pediatric hematology oncology fellowship by the National Board of Exams. A key initiative was the Indian National Training Project in Practical Pediatric Oncology organized to train pediatricians, pediatric surgeons, and postgraduates in the early recognition of childhood malignancies and to prepare them for ‘shared’ care of these children [35]. There was no collaborative research or clinical trials conducted during this period under the aegis of PHO IAP.

The earliest report of collaboration in the field of pediatric oncology in India was that between Cancer Institute, Chennai and the National Cancer Institute, USA in the early 1980s. Adopting a more intense protocol (MCP841) than that being used at the time, led to an improvement in the event free survival of acute lymphoblastic leukemia from 20% to 40% [36]. This treatment strategy was then adopted by Tata Memorial Hospital, Mumbai in 1986 and All India Institute of Medical Sciences, New Delhi in 1992 [37]. With this common protocol, event free survival rates of 40–60% were achieved and result of this landmark collaboration, remains the only published prospective multi-centre interventional study related to childhood cancer from India till date [37].

As we entered the 21st century, the scientific output of the Indian pediatric oncology community began to surge in the form of scientific presentations and publications [38,39]. However, these were of relatively low scientific quality and there was a glaring absence of multicenter studies [38,39]. Around the same time, but distinct from these “scientific” efforts, philanthropic initiatives partnering with treatment centres became increasingly prevalent in India. These not only supported the medical treatment, but also provided more holistic support with nutritionists, nurses, social workers, logistics, data managers, etc. The most recognizable among these were JivDaya Foundation and Cankids … Kidscan, both of whom had a national footprint [40]. Although even here, collaborative research or clinical trials was not an area of focus, their efforts brought individuals from across India together and the additional resources like databases, data managers, nurses, etc. made the start of collaborative research more viable.

3. Indian Pediatric Oncology Group (InPOG)

The need to establish a national cooperative group in order to develop prospective multi-centre clinical trials in India became increasingly apparent. Such a strategy was critical to understand the biological differences in the disease, to assess responses to treatment and ultimately to improve childhood cancer survival in India. With this goal in mind, some members of the PHO IAP led by Dr Bharat Agarwal, Dr Purna Kurkure and Dr Anupam Sachdeva formed InPOG in 2008 [41]. The mission of InPOG is to improve the outcomes of children with cancer in India by collaborative research. The focus during the early years of InPOG was to put the systems in place to allow the running of such a group.