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Retinoblastoma: One World, One Vision

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Abstract

Retinoblastoma is curable when diagnosed early and treated appropriately; however, the prognosis is dismal when the basic elements in diagnosis and treatment are lacking. In developing countries, poor education, lower socioeconomic conditions, and inefficient health care systems result in delayed diagnosis and suboptimal care. Furthermore, the complexity of multidisciplinary care required is seldom possible. While ocular salvage is a priority in the Western world, death from retinoblastoma is still a major problem in developing countries. To bring the two ends of this spectrum together and provide a forum for discussion, the *One World, One Vision* symposium was organized, where clinicians and researchers from various cultural, geographic, and socioeconomic backgrounds converged to discuss their experiences. Strategies for early diagnosis in developing countries were discussed. Elements in the development of retinoblastoma centers in developing countries were discussed, and examples of successful programs were highlighted. An important component in this process is twinning between centers in developing countries and mentor institutions in high-income countries. Global initiatives by nongovernmental organizations such as the International Network for Cancer Treatment and Research, Orbis International, and the International Agency for Prevention of Blindness were presented. Treatment of retinoblastoma in developing countries remains a challenge. However, it is possible to coordinate efforts at multiple levels, including public administrations and nonprofit organizations, to improve the diagnosis and treatment of retinoblastoma and to improve the outcome for these children.

Introduction

Progress in clinical sciences is usually measured in terms of the advances made in well-developed countries, where higher education, research, and excellent health care converge to provide the circumstances necessary to advance. This is also true for childhood cancer; in the past two decades, we have witnessed important advances in the field of pediatric oncology, and survival rates in excess of 75% are now reported. (1) However, we cannot ignore the fact that 80% of children with cancer live in developing countries; treatment options for them are limited, and cure rates are very low. True advances will not have been made until the benefits are extended to all children.

Despite its rarity, retinoblastoma exemplifies many of the aspects that make pediatric cancer a unique health problem. Although it is very curable when diagnosed early and treated appropriately, the prognosis is dismal when the basic elements in diagnosis and treatment are lacking. Furthermore, retinoblastoma is the paramount example of multidisciplinary care in pediatric cancer, and in contrast to other malignancies, it is not possible to advance in the treatment of this disease without the participation of multiple specialists, usually difficult to achieve even in developed countries. Disparities in education and socioeconomic conditions, coupled with inefficient or suboptimal health care, result in immense differences in outcomes. Whereas ocular salvage is the primary concern in the Western world, death from retinoblastoma is still common in developing countries. In this scenario, there is no common ground to facilitate a progressive transfer of knowledge to improve outcomes in countries with limited resources.

To bring the two ends of this spectrum together and provide a forum for discussion, the *One World, One Vision* symposium was organized, and clinicians and researchers from various cultural, geographic, and socioeconomic backgrounds converged to discuss their experiences and problems. The 2-day symposium (January 25–26, 2007) was attended by pediatric oncologists, ophthalmologists, and other health care workers from North, Central, and South

America, Europe, Africa, and Asia (scholarships were awarded to participants from developing countries).

The symposium opened with an overview of pediatric cancer worldwide, including an analysis of disparities between countries with differing resources, and discussion of the concept of twinning, whereby institutions in developed countries mentor programs in countries with limited resources.

Pediatric Cancer Worldwide: Twinning is Winning (Raul C. Ribeiro, Director International Outreach Program, St. Jude Children's Research Hospital)

There are obvious contrasts between developed and developing countries in their resources and approaches to children with cancer. In developed countries, children with cancer benefit from a quality multidisciplinary approach and supportive care, risk-adjusted intensive treatments, cooperative trials, and molecular diagnosis that facilitates molecular targeted therapies. Importantly, cure at all costs may be the ultimate focus, and long-term follow-up has become a research activity. The landscape is quite dissimilar in developing countries, where 80% of the 160,000 newly diagnosed cases of childhood cancer each year occur. Lack of access to care, scarcity of human resources, unavailability of essential medications, inadequate infrastructure, lack of support from government and international nongovernmental organizations, and lack of cancer registries result in significantly lower expectations. One of the most successful strategies to improve cure rates is twinning. Elements for twinning include an existing pediatric hematology-oncology unit, community support, and close communication with a mentor program in a developed country. The main goals of twinning initiatives are to develop pediatric cancer units; facilitate alliances among governments, private–sector institutions, and nongovernmental organizations; and establish best medical practices. Eventually, the new programs should become able to participate in collaborative research projects. This model has proven very successful, and examples of marked improvement in the outcome for children with cancer in Central and South America and in the Middle East were presented (2–4).

Following this introductory lecture, Dr. Judith Wilimas moderated the first session, ***Retinoblastoma: Where are we now?***, in which Drs. Leslie L. Robison, Carlos Rodriguez-Galindo, Matthew W. Wilson, Thomas E. Merchant, Patricia Chevez-Barrios, and Michael A. Dyer provided an update on our current knowledge of the biology, epidemiology, clinical characteristics, and treatment of retinoblastoma.

The second session, ***Retinoblastoma in the Developing World***, was moderated by Dr. John Hungerford, Consultant Ophthalmologist at Moorfields Eye Hospital and St. Bartholomew's Hospital, London. In low-income countries, cure rates for retinoblastoma are less than 50%, and vision preservation is minimal, primarily because of advanced disease at the time of diagnosis. Early diagnosis is critical for improving survival and vision preservation. Abandonment and refusal of therapy also hinder advancing survival rates. The importance of public health campaigns to improve diagnosis and early referrals cannot be overstated, and examples of the effect well organized national programs can have on public health were presented (Table 1).

Improving Diagnosis: Retinoblastoma Awareness Campaign in Honduras (Dr. Ligia Fu, Hospital de Niños, Tegucigalpa, Honduras)

Delayed diagnosis is a common feature in pediatric cancer in Central America, where social, cultural, and economic barriers converge to adversely affect health care. Retinoblastoma, like pediatric cancer in general, is not a priority in developing countries, and support from health

administrations for early diagnosis initiatives is unlikely. For this reason, the awareness campaign in Honduras was designed to be linked to yearly vaccination campaigns, which try to achieve greater than 95% immunization coverage for young children. Since 2003, posters and flyers were distributed during the annual vaccination campaigns, and health care workers were educated about retinoblastoma. In total, 22,000 posters were distributed over a 2-year period, with access to all 1414 National Health Centers. It is estimated that 500,000 parents were informed. Primary care physicians and nurses were provided with educational materials. The estimated cost of the posters and flyers was approximately $2,700 per year, and the campaign was sponsored by the Honduran Foundation for Children with Cancer, the International Union Against Cancer, and the Honduran government. The effect of this campaign was tremendous, with an increase in the number of patients being referred to the pediatric oncology unit, a decrease in lag time (from 7.2 months to 5.5 months), and a significant decrease in the number of extraocular cases (from 73% to 35%) (5).

Impact of Public Health Campaigns on Retinoblastoma Related Mortality (Dr. Célia Antonelli, Hospital do Câncer A.C. Camargo, São Paulo, Brazil)

The incidence of retinoblastoma in Brazil is not uniform, ranging from less than 2 cases per million children per year in the cities of Fortaleza and Belém (Northern Brazil) to more than 11 cases per million in Campinas (Southeast). However, retinoblastoma-related mortality does not follow the same geographic variations. From 1980 to 2002, retinoblastoma mortality rates were lower in the city of São Paulo than in the states with a lower incidence, suggesting disparities in time to diagnosis and access to medical care (6). Furthermore, between 1975 and 1985, as many as two thirds of patients nationwide presented with extraocular disease. Strategies to improve early diagnosis were developed at three levels: 1) flyers and posters that were distributed in the main streets of São Paulo; 2) training of primary school teachers, with more than 1000 seminars presented in more than 100 schools over 5 years; and 3) specific training on retinoblastoma for medical students and primary physicians. After the initiative, extraocular retinoblastoma decreased from 56% in 1985 to less than 10% in 2003. However, geographic differences remained. The greatest decrease of extraocular disease occurred in the richer states of the Southeast, but no dramatic effect was seen in the poorer Northeast, where close to 50% of the patients still presented with extraocular disease. Nonwhite patients, age > 24 months, and lag time > 6 months were all significantly correlated with extraocular disease (6). Advances in the management of extraocular retinoblastoma by Brazilian investigators contributed greatly to these improvements (7;8). Any public health strategy should consist of education of health professionals and lay population, development of regional centers of excellence, and universal health care access.

National Programs: Grupo Mexicano de Retinoblastoma (Dr. Carlos Leal-Leal, Instituto Nacional de Pediatría, Mexico City, Mexico)

The Grupo Mexicano de Retinoblastoma (RtbMex) program was created in January 2003, arising from the need to coordinate the efforts of organizations interested in improving care for retinoblastoma patients. The group performed a retrospective review of the experience of 16 institutions from January 1997 to December 2002 (9). A total of 500 retinoblastomas were diagnosed during that period. The median age was 28 months for patients with unilateral disease and 14 months for patients with bilateral disease. Approximately one third of the patients had extraocular disease at diagnosis. The estimated 5-year disease-free survival rate was 85%. The lag time for patients with advanced disease was more than 12 months. A National Retinoblastoma Registry was created with the participation of 27 centers. Early diagnosis and education were priorities; a large public education campaign was developed with posters in public places, schools, and health care centers. A major initiative included the education of

health care professionals, with seminars and printed materials. The group developed a national protocol with guidelines for the management of retinoblastoma. RtbMex continues to work with annual national and regional meetings, a national early diagnosis campaign, and updates for the national treatment protocol. As in many developing countries, financial resources for cancer control are limited. Only half the population of Mexico has health insurance coverage; thus, funds must be provided from alternative sources for more than 50 million individuals. Some of the financial limitations to improving medical care for children with cancer will be resolved with the implementation of a plan from the federal government (that includes an agreement with the Mexican tobacco industry) to provide medical coverage for all uninsured Mexican children with cancer (10). With this initiative ("Seguro Popular"), RtbMex will be able to make the national protocol and early diagnosis initiatives available to a wider population.

Treatment of retinoblastoma requires a multidisciplinary team of well trained specialists, and efforts must be made to supply developing countries with the resources necessary to provide such care. This can be achieved through twinning. In the session ***Developing a Retinoblastoma Centre: Twinning Models***, two successful examples of this approach were presented (Table 1).

Brachytherapy Program in Guatemala (Dr. Margarita Barnoya, Unidad Nacional de Oncologia Pediátrica, Guatemala City, Guatemala)

Guatemala exemplifies the challenges in the creation of oncology centers in developing countries. Guatemala is an ethnically diverse country; 22 Mayan languages are spoken, 42% of the population is illiterate, and the infant mortality rate in some areas is as high as 38%. Although epidemiologic studies are lacking, there is a perception that retinoblastoma is more common in Central America than in other locations. Multiple cultural barriers and poverty traditionally result in very high abandonment rates; 26% of patients with retinoblastoma abandon treatment, often before enucleation. A center of reference with a multidisciplinary team was developed at Roosevelt Hospital in Guatemala City. Patients from other Central American countries are referred there when specialized care is needed. The center has been equipped with a RetCam retinal imaging system, cryotherapy tools, and a diode laser for thermotherapy. All cases are discussed with the St. Jude team using the Orbis Cyber-Sight e-consulting system. The National Pediatric Oncology Unit is part of the Association of Pediatric Hematologists and Oncologists of Central America, and a protocol for the management of retinoblastoma was developed in collaboration with other institutions. Improvements in the diagnosis and conservative management of intraocular retinoblastoma led to the need for more sophisticated therapies, and a brachytherapy program was established under the supervision of the mentor institution. Additional initiatives of the group include an early diagnosis campaign with education of rural health care workers.

Building a Center of Excellence: The King Hussein Cancer Center Program (Dr. Ibrahim Qaddoumi, Department of Pediatric Oncology, King Hussein Cancer Center, Amman, Jordan)

Before the program was developed, there was no standard of care in the country; patients would undergo enucleation or irradiation, and there was no team approach. Retinoblastoma mortality was 38%, and the enucleation rate for patients with bilateral disease was 92%. The four major components of the program were: 1) identification of existing resources, 2) development of a multidisciplinary team, 3) identification of a modern center that could mentor the newly developed group using a twining model, and 4) the use of telemedicine for continuing education and consultation. For a twinning model to be successful, the relationship must be systematic,

modern communication technology should be used, exchange visits should be facilitated. A pivotal element of this twinning model is telemedicine. Electronic correspondence, Orbis Cyber-Sight e-consultation, and videoconferencing were all used. Technology transfer included the acquisition of cryotherapy equipment and a diode laser for thermotherapy. Under the new program, the enucleation rate in bilateral cases dropped to 26%, with no patients requiring bilateral enucleations. The benefits of the program also included standardization of therapy, better pathology interpretation, development of local leaders, and a spillover effect to other services. An important point of telemedicine is that, although there is still a learning curve, patient care is improved immediately.(11)

As these centers of excellence grow, the impact can be seen in the care of children with retinoblastoma worldwide. In the session ***Centers of Excellence in Developing Countries: Integrating State of the Art Treatment and Research***, examples of state of the art centers were presented (Table 1).

The Sankara Nethralaya Foundation (Dr. Tarum Sharma, The Sankara Nethralaya Foundation, Chennai, India)

The Sankara Nethralaya Foundation is a not-for-profit organization that aims to provide quality eye care for the less fortunate. The institute sees more than 1500 patients and performs 125 surgeries daily. This institution has also focused on the development of a modern center for retinoblastoma. Their experience in the management of 355 patients has been recently published (12) (13). Over the years, a center with modern treatments and technology has been developed, and the results have been outstanding. As a continuation of the clinical program, a translational research initiative developed. Investigators there have contributed significantly to the field of multi-drug resistance protein expression (14), showing that 38–58% of tumors express MDR proteins such as P-gp and LRP without correlating with histologic findings such as choroidal invasion, differentiation, and response to chemotherapy. Additionally, research has been performed on retinoblastoma stem cell marker expression (15), showing that invasive tumors express more ABCG2 and MCM2 proteins. Molecular analysis and sequencing of the *RB1* gene are also available, thus facilitating genetic counseling and providing the first steps toward a more comprehensive molecular characterization of retinoblastoma (16).

The Hospital Garrahan Translational Research Program (Dr. Guillermo Chantada, Hospital Nacional de Pediatría Dr. J.P. Garrahan, Buenos Aires, Argentina)

The retinoblastoma program at Hospital Garrahan started in the late 1980s with the development of the first prospective protocol for patients with retinoblastoma, covering up to 85% of affected patients in Argentina (17). A retinoblastoma center was established over the next decade under the mentoring of Dr. David Abramson and twinning with Memorial Sloan-Kettering Cancer Center in New York. Studies performed by this group have provided the most relevant information in histopathologic risk characterization of retinoblastoma and in the definition of adjuvant therapy (18–20), also resulting in a consensus international retinoblastoma staging system (21). A multidisciplinary translational research program has been developed, including ocular pharmacology and tumor cell biology programs. The integration of parental groups into research activities, helping with funding and raising awareness in retinoblastoma research, provides a model to be followed. The current retinoblastoma research program includes: 1) an early detection program; 2) a chemoreduction and eye salvage protocol (22); 3) developmental therapeutics, with studies on the intraocular penetration of topotecan by periocular administration (23); and 3) detection of minimal residual disease by PCR amplification of GD2 synthase in bone marrow (24).

In the second session of the day, ***Programs of Global Impact***, strategies to improve diagnosis, treatment, and outcome at a global level were presented and discussed.

The International Network for Cancer Treatment and Research (Dr. Sidnei Epelman, São Paulo, Brazil)

The International Network for Cancer Treatment and Research (INCTR) is a not-for-profit, nongovernmental organization founded in 1998 by the International Union Against Cancer and the Institut Pasteur in Brussels to address cancer with a global vision (www.inctr.org). The U.S. National Cancer Institute provides financial, technical, and intellectual support. The INCTR, in turn, assists developing countries through a structured program of research collaboration, education, and training to develop an increased understanding of the causes of and predisposition to regionally important cancers and to increase survival rates and the quality of life in patients with cancer. The INCTR retinoblastoma strategy group was formed in November 1999. A first evaluation of the situation in developing countries showed late presentation of patients, a lack of professional awareness, and a need to develop strategies for advanced retinoblastoma. Subsequent meetings took place between 2001 and 2005, and three strategies were developed: 1) development of the survey study, “Understanding Problems Faced by Parents of Children with Retinoblastoma”; 2) development of strategies to improve early detection through public and professional awareness; and 3) development of a treatment protocol for patients with extraocular, non-central nervous system metastatic disease. INCTR-sponsored public awareness campaigns were developed in Brazil; Mexico, where the INCTR also supported the creation of the RtbMex group; and India, where retinoblastoma awareness was boosted by a movie based on the true story of a child with bilateral retinoblastoma (*Shwaas* [Breath], Sandeep Sawant, Director, Best Feature Film of 2004 in India, selected as India’s official entry for the 77th Academy Awards). Thirteen institutions representing 10 developing countries, and 388 individuals participated in the survey responded to the survey. Very relevant information was obtained; after the first symptom, two thirds of the patients sought advice or help, but one third of health care providers continued to observe the child. After the first visit, although most patients followed the advice given and were referred to a specialist, 27% still sought a second opinion. Children from rural areas had more advanced disease, and parental education level was negatively associated with disease stage. Longer intervals between the first sign/symptom and the diagnosis were associated with higher disease stages and lower parental education. Future INCTR initiatives include a proposal for Retinoblastoma Day and the organization of a Latin American meeting for discussion of epidemiology, screening, and early diagnosis.

Orbis International (Dr. Eugene Helveston, Ophthalmologist-in-Chief, Orbis International)

ORBIS international (www.orbis.org) is a not for profit, non-governmental organization whose mission is the elimination of preventable blindness worldwide. Starting in 1982, ORBIS launched a DC8 aircraft equipped with an operating theater, classroom, and procedure room. In 1994 this aircraft was replaced with a DC10 which is maintained by FedEx. The ORBIS Flying Eye Hospital has visited 85 countries, conducting hundreds of two to three-week programs offering skills transfer, and teaching local professionals the latest and most effective techniques in surgical and medical treatment of eye diseases. A new initiative has been the development of an internet-based program called ORBIS Telemedicine, Cyber-Sight. This program features E-Consultation, which facilitates communication and mentorship between health care workers in developing countries and specialists in state of the art centers in developed countries. The E-Consultation program allows sharing clinical information (including images) with experts (mentors) that have been designed for specific eye diseases

(i.e. retino-vitreal diseases, glaucoma, ocular oncology, etc.). Once the case file has been submitted by a partner, a mentor receives e-mail notification, reviews the case, and provides immediate advice. The file can remain open for additional communication between the partner and mentor. These resources have been pivotal in the development of the retinoblastoma centers in Guatemala and Jordan described above. In both centers, all retinoblastoma cases are reviewed by the team of experts at the mentor institution, providing immediate advice on each case, and continuing education.

International Agency for Prevention of Blindness (Dr. Louis D. Pizzarello, Secretary General)

The International Agency for Prevention of Blindness (IAPB) was founded in 1975 and is formed by 100 organizations dedicated to blindness prevention. With the recognition that blindness is the sixth most common cause of disability worldwide, the agency launched the Vision 2020 program in 1990 as a joint initiative between World Health Organization and IAPB to lead a global effort to eliminate avoidable blindness by 2020 (25). The plan is to set up a unit at a district level (1–2 million people) with an ophthalmologist, primary care facilities, surgery for cataracts and other conditions, and possible referral to tertiary centers. Disease strategies include cataracts (the most common cause of blindness in the world), trachoma, onchocerciasis, refractive errors, diabetic retinopathy, glaucoma, and childhood blindness. There are 1.4 million blind children in the world, with 500,000 newly blind children each year. Childhood blindness is responsible for one third of the $42 billion lost each year to avoidable blindness. In market economies, the blindness rate is 0.25 per 1000 children, and the most common causes are retinopathy of prematurity and genetic diseases. In midlevel economies, blindness rates are 0.5 per 1000, and the most common causes are congenital cataracts and glaucoma. Finally, in very poor economies, the blindness rate is 1.0 per 1000, and it is mostly due to vitamin A deficiency and measles. It is in this group that public health measures (e.g., nutrition, immunizations, and vitamin supplementation) can make the greatest difference. An example is vitamin A fortification of sugar in Honduras. As the Vision 2020 program grows, the plan is to strengthen existing programs and develop centers of excellence. Fostering collaborations between businesses, nonprofit agencies, and health and social development agencies is being championed as a powerful strategy to achieve success that would otherwise be impossible for independent entities working alone.

The complexity of retinoblastoma treatment can be understood only in the context of the huge disparities between high- and low-income countries. Similar clinical situations may require different approaches depending on the context in which they occur. In the last session of the day, a discussion was organized around the disparities in health care for children with retinoblastoma in developed and developing countries. The discussion centered on the definition of standard of care and the characterization of factors that affect existing standards.

Ethical Decision Making in the Care of Seriously Ill Children (Dr. Javier Kane, Director of St. Jude's Palliative and End-of-Life Care Program, and Dr. Raymond Barfield, Chair of St. Jude's Ethics Committee)

Defining a standard of care that is meaningful for developed and developing worlds alike is challenging. Does "standard of care" imply the provision of treatment with curative intent according to best clinical evidence? Is it the last published paper with the best clinical outcomes? Is the "standard of care" the same as the "standard of curative therapy"? Who defines the standard of care, and how is it defined? Is it in terms of disease only, or is it attending to the needs of the child and family within a particular context? If so, what factors influence the standard of care and the decision-making process?

A discussion was organized around hypothetical cases in contrasting socioeconomic scenarios. A "high-income" country was defined by an annual income of $38,000 *per capita* and 1.8 physicians per 1000 population. An experienced pediatric oncologist sees 15 patients per day, and resources are widely available. In contrast, the "low-income" country had an annual income of $500 *per capita* and only 0.25 physicians per 1000 population. An experienced pediatric oncologist sees 100 patients per day, and the infrastructure is deficient. Are the standard of care and standard of curative therapy the same for both countries? This is relevant in the management of patients with retinoblastoma. In the "high-income" country, lifesaving therapy is accessible, courts may override parental refusal of treatment, and supportive care services are available. In contrast, in the "low-income" country, although lifesaving therapy is accessible, there might be a stigma attached to blindness, which leads to high rates of therapy abandonment. Early detection programs are needed in both countries, but the effect on lifesaving may be greater in the "low-income" country, whereas eye and vision preservation may be improved more in the "high-income" country. In the "high-income" country, there may be cultural pressure to "do everything to achieve cure," whereas in the "low-income" country, resources are limited and are usually allocated to health problems that are more prevalent than pediatric cancer. Hospital administrators often believe that, in a resource-limited environment, less money will be available for diseases with more certain cures if a child with an uncertain prognosis is treated. Finally, cultural barriers cannot be ignored; is it legitimate for a cultural stigma to override the use of curative therapy, and how does international pressure influence local physicians to overcome these obstacles?

The second day was organized around two roundtables, open for discussion and participation by all attendees. In the first roundtable, Drs. Michael A. Dyer, Joan O'Brien, Patricia Chevez-Barrios, and Linn Murphree led a discussion on translational research and the finding of best therapies for intraocular retinoblastoma and eye salvage approaches.

Translational Research In Retinoblastoma

The field is moving toward identifying agents with good intraocular penetration and exploring methods of local delivery. Better understanding of retinoblastoma biology is also leading to the exploration of molecular targets, such as inhibitors of MDMX/p53 interaction (26) and suicide gene therapy. (27). A challenging question is whether current approaches, which include chemotherapy and aggressive focal treatments, offer a significant advantage over the use of radiation therapy alone in terms of eye salvage and vision preservation. Are we making a simple disease more complex to treat with the incorporation of chemotherapy? Retinoblastoma treatment has moved away from radiation therapy, and yet we should pause and evaluate what has happened to the field of radiation oncology in the interim. With the increasing availability of proton beam radiation therapy new opportunities for the treatment of intraocular retinoblastoma are emerging.

Practical Steps to Develop a Retinoblastoma Program

The second roundtable, moderated by Drs. John Hungerford, Matthew W. Wilson, and Carlos Rodriguez-Galindo, focused on building a retinoblastoma program. The "retinoblastoma problem" may be different in each country, and a detailed analysis of the situation must be performed before priorities are set (Table 2).

1. *What is my retinoblastoma problem?* Different scenarios may apply to each country or center, and the recognition of the main problem is the first step toward the development of a program. In many developing countries, the problem is late diagnosis, which can be due to cultural or socioeconomic barriers or due to a lack of information at the primary care level. Another key point is poor referral to an oncology unit; a delay may be caused by a deficient health care system or a lack of recognition

of the existence of a retinoblastoma center. A third common problem is the lack of a retinoblastoma program; that is, lack of the infrastructure, training, multidisciplinary team culture, and support by hospital administration that are required for a successful program.

2. *What are the priorities?* As for any pediatric oncology program, the first priority is to cure, to save lives. In many instances, the first step toward making a difference is to invest in early detection campaigns and education of primary health providers and health agents and to facilitate a referral network. Very often, the main obstacle to cure is refusal of enucleation, and special strategies designed to bridge the cultural gap and overcome the stigma associated with this procedure must be devised. As diagnosis improves and a referral pattern is established, the development of a retinoblastoma program becomes the necessary next step. For a successful program to develop, a careful evaluation of the context (hospital and community support) and a needs assessment (team and infrastructure) must be performed, and efforts must be unified.
3. *Building a team*. Treatment of retinoblastoma can be successful only if a multidisciplinary approach is taken. Pediatric oncology, ophthalmology, radiation therapy, nursing, pharmacy, occupational therapy, and social work must work together in a "team culture." Only through the coordinated efforts of multiple specialists can a modern, effective retinoblastoma center be built.
4. *Twinning is winning*. Developing a treatment center requires time. However, the learning curve can be shortened by adopting a twinning model and using communication technology that facilitates mentorship and supervision. The responsibility of improving cancer care in developing countries must be shared, and high-income countries must be involved in helping those less fortunate.

Discussion

Like many pediatric diseases, and cancers in particular, retinoblastoma remains a major challenge in developing countries. However, it is possible to coordinate efforts at multiple levels, including public administration and nonprofit organizations, to improve diagnosis, treatment, and outcome for these unfortunate children. Developed countries must assume a responsible role in narrowing the gap between the industrialized world and the less fortunate. We must continue to work toward providing all children the same opportunities for cure: *One World, One Vision*.

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Table 1

Retinoblastoma Programs in Developing Countries

	Initiative	Impact	Lessons learned
Honduras	Awareness campaign linked to an immunization campaign	- Increased referrals - Decreased lag time - Decreased extraocular disease	**- Low-cost awareness campaigns can be linked to other public health initiatives**
Brazil	Early diagnosis campaign targeting general public, school teachers and health care providers	- Decreased extraocular disease and lag time - Decreased retinoblastoma mortality	**- Importance of education of lay population, teachers, and health care providers**
Mexico	- Development of a National Retinoblastoma Program - Early diagnosis initiatives in multiple states - Referral network - Treatment guidelines	- Decreased delayed diagnosis - Improved quality of care - Visibility of a retinoblastoma program	**- Importance of national programs with initiatives at a multi-state level and creation of referral network**
Guatemala	- Twinning with a retinoblastoma center - Development of a retinoblastoma center of excellence with a multi-disciplinary team	- Improved diagnosis and treatment - Development of a regional center of excellence	**- State of the art centers are possible in developing countries** **- Regional centers of reference can be developed**
Jordan	- Use of telemedicine for continuing education and consultation	- Spill over effect to other services that may benefit of twinning	**- Twinning with institutions in more developed countries is a model to follow** **- Use of telemedicine accelerates learning**
India **Argentina**	Development of integrated clinical and translational research programs	- Contributions to the retinoblastoma biology and treatment fields	**- Contributions from clinical and translational researchers in developing countries may have a major impact in retinoblastoma research and treatment**

Table 2

Building a Retinoblastoma Program

Elements	Analysis
The Retinoblastoma “Problem”	Late diagnosis - Cultural or socioeconomic barriers - Lack of information at primary care level Poor referral to oncology units - Deficient health care system - Lack of recognition of a retinoblastoma center Lack of a Retinoblastoma program - Lack of multidisciplinary approach - Lack of infrastructure - Fragmented care
The Priorities	- Early detection campaigns and education of primary health care providers - Overcome stigma associated with enucleation - Develop a referral network - Development of a retinoblastoma program
Building a Team	- Multidisciplinary team approach is a must - Members: Pediatric oncology, ophthalmology, radiation oncology, pharmacy, nursing, occupational therapy, social work
Twinning	- Mentorship, training, and supervision - Use of telemedicine and electronic communication