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Intra-Arterial Chemotherapy for Retinoblastoma: A Collaborative Effort

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A B S T R A C T

Approximately 300 children in the United States are diagnosed yearly with retinoblastoma. For a generation, it has had the highest cure rate among pediatric solid tumors, allowing reduction in side effects of management to become important determinants of therapy. Priorities of treatment are saving life, eyes, and vision. Standard treatment involves enucleation, multiagent systemic chemotherapy, and radiation and intra-arterial chemotherapy (IAC). IAC is a treatment option to deliver chemotherapy locally to the eye while minimizing systemic exposure. Research in the treatment of retinoblastoma has led to new treatment protocols for children. The purpose of this article is to define retinoblastoma, introduce the goals and priorities of retinoblastoma treatment, and describe the standard of care treatment options with a focus on IAC, which is administered in interventional radiology. It also highlights important nursing issues including the administration of chemotherapy in a clinical area where it is not traditionally administered and the challenges faced in caring for children and families with retinoblastoma.

Introduction

Retinoblastoma is the most common malignant primary intraocular tumor that arises in the retina and accounts for approximately 3% of all worldwide pediatric cancers (Efren, Monroy, Orbach, & Vanderveen, 2014; Rodriguez-Galindo, Orbach, & VanderVeen, 2015). It is a cancer seen most often in very young children, as two-thirds of all cases are diagnosed before 2 years, and is rarely seen in children older than 5 years (Rodriguez-Galindo et al., 2015). Retinoblastoma has a 95% survival rate in the United States, which has allowed for the evolution of disease management toward a more risk-adapted approach, with the goal to optimize saving lives, eyes, and vision while minimizing short-term and long-term toxicities (Rodriguez-Galindo et al., 2015). In less developed countries where there is greater tumor burden, reported survival rates remain as low as 0% to 5% (Singh & Daniels, 2016). The incidence of retinoblastoma is disproportionally distributed around the world with higher rates found in Africa, India, and in children of Native American descent in North America (Rodriguez-Galindo et al., 2015).

Intra-arterial chemotherapy (IAC) is a treatment option for retinoblastoma that is improving ocular survival and visual acuity, with fewer and less severe systemic complications than systemic chemotherapy or external beam radiation (EBR) (Efren et al., 2014). The purpose of this article is to define retinoblastoma, introduce the goals and priorities of retinoblastoma treatment, and describe the standard of care treatment options with a focus on IAC, which is administered in interventional radiology (IR). It also highlights important nursing issues including the administration of chemotherapy in a clinical area where it is not traditionally administered and the challenges faced in caring for children and families with retinoblastoma.

IAC requires a well-coordinated multidisciplinary approach to assure safe delivery of chemotherapy in a nononcology setting. These children require frequent evaluations by oncology ophthalmologists, pediatric oncologists, pediatric neurointerventional radiologists, anesthesiologists, interventional radiologists, oncology registered nurses (RNs) and nurse practitioners, and psychosocial providers. The multidisciplinary team approach is critical to minimize the inherent risks of delivery of chemotherapy in a nononcology setting, such as chemotherapy errors, and minimize risks

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of the IR procedure itself, including stroke and bleeding (Efren et al., 2014). At Dana Farber/Boston Children's Cancer and Blood Disorders Center, IR and oncology nurses assume a leadership role in this process.

Pathogenesis

The pathogenesis of retinoblastoma involves the inactivation of both alleles on the *RB1* gene, allowing for tumors to develop. There are two clinical forms of retinoblastoma. Heritable retinoblastoma is defined by the presence of a germ line mutation of the *RB1* gene, which may have been inherited (25%) or occurred as a de novo mutation early in embryogenesis (Rodriguez-Galindo et al., 2015). Children with the heritable form are typically diagnosed at an early age (median time to diagnosis, 14–16 months) and present with bilateral or unilateral multifocal disease (Rodriguez-Galindo et al., 2015). Children with an RB1 germ line mutation may continue to develop new tumors after diagnosis and treatment and need frequent examinations for years (Rodriguez-Galindo et al., 2015). These children are also at a higher risk to develop secondary malignancies later in life, secondary to their germ line mutation, and this risk increases after treatment with radiation and chemotherapy (Rodriguez-Galindo et al., 2015). The nonheritable form is defined by a sporadic mutation to both alleles in a somatic cell. Children with this form typically present at an older age (median time to diagnosis, 29–30 months) and present with unilateral unifocal disease. They are not at risk to develop secondary malignancies later in life (Rodriguez-Galindo et al., 2015). All children with retinoblastoma are referred for genetic counseling to assist parents in understanding the genetic consequences of each form of retinoblastoma, estimate the risk in relatives, and test for the presence of a germ line mutation (Rodriguez-Galindo et al., 2015).

Early detection of retinoblastoma is critical to the treatment options as it allows for identification of the disease while it is still intraocular (Rodriguez-Galindo et al., 2015). There are a variety of treatment options for retinoblastoma, including several vision-sparing therapies (Rodriguez-Galindo et al., 2015). Factors influencing treatment choice are the tumor size and location, visual prognosis, the presence or the absence of vitreous or retinal seeds, age and genetic status (Rodriguez-Galindo et al., 2015). Treatment options include enucleation, focal therapies (cryotherapy and laser), radiation therapy (EBR or proton beam), systemic chemotherapy, IAC, and intravitreal chemotherapy (Rodriguez-Galindo et al., 2015). A review of the literature shows that treatment for retinoblastoma, especially bilateral disease, has evolved to be more focused on globe salvage and some vision preservation.

Although the first report of IAC was in 1958, Gobin, Dunkel, Marr, Brodie, and Abramson (2011) began using selective ophthalmic artery infusion in 2006 at their institution and with a decade of experience have shown that IAC could be successful in avoiding enucleation and EBR therapy, with acceptable ocular toxicity and minimal systemic side effects (Efren et al., 2014; Gobin et al., 2011). In Gobin center, they have replaced systemic chemotherapy and EBR, both of which have many potentially serious adverse effects, with IAC for tumors too large to be controlled with focal therapies alone (Gobin et al., 2011). Gobin et al. (2011) reported that catheterization succeeded in 98.5% of all procedures. Ocular event-free survival rates at 2 years were 70% for all eyes, 81.7% for eyes that received IAC as their primary treatment, and 58.4% for eyes that had previous treatment with chemotherapy or EBR (Gobin et al., 2011).

Munier et al. (2017) compared outcomes of advanced unilateral disease treated with systemic chemotherapy to first-line IAC. Globe retention was 100% in the IAC group as compared with 57% in the systemic chemotherapy group. No metastasis or deaths occurred in either group, and IAC was associated with fewer side effects, faster and more extensive response rates, fewer relapses, and better visual acuity than the systemic chemotherapy group. They concluded that IAC should be considered the treatment of choice in Group D unilateral retinoblastoma (Murphree, 2005; Rodriguez-Galindo et al., 2015). Abramson, Marr, and Francis (2016) performed a single-institution retrospective study of all Group D eyes treated with IAC from 2006 to 2012. This study concluded that IAC is a very effective treatment for Group D retinoblastoma and appears to have rates of globe salvage much greater than systemic chemotherapy without compromising patient survival (Abramson et al., 2016). IAC can be performed multiple times, using multiple chemotherapeutic agents on one or both eyes, with an acceptable side-effect profile (Abramson et al., 2016).

IR Procedure

Performing neuroradiology interventions in children necessitates a well-orchestrated team approach to ensure patient safety and optimal patient outcomes. Nurses take the lead on facilitating communication across the care team. Members of the multidisciplinary team need to have a shared understanding of the inherent risks. Because retinoblastoma is a disease of young children, the unique neurovascular anatomy and physiology of these children make neuroradiology procedures more challenging than in adults. It is critical that steps be taken to mitigate the risks that pediatric neurointerventional procedures present (Ashour & Orbach, 2015).

These types of neurointerventional procedures require total patient immobility and are done under general anesthesia using paralytics with the anesthesia team providing breath holding as needed. Systemic anticoagulation is typically administered to decrease the potential risk of thromboembolytic stroke or ischemic injury (Rodriguez-Galindo et al., 2015). In addition, obtaining femoral arterial access in a small child may increase the risk of lower extremity ischemic complications. Therefore, the smallest possible femoral sheath is used for arterial access. Because of limitations in the amount of contrast that can be given based on the child's weight, the neuroradiologist must be judicious with contrast administration (Orbach et al., 2014).

IAC is performed under fluoroscopic visualization so these patients are unavoidably exposed to ionizing radiation. There is increasing evidence that children are more vulnerable and have an increased risk of developing secondary tumors (Orbach et al., 2014). Optimized radiation exposure techniques are used by the neuroradiologist whenever possible. As the use of IAC for pediatric retinoblastoma emerged, we were additionally challenged to develop an interdisciplinary process to support the management of chemotherapy in IR where chemotherapy was not traditionally delivered. This required developing a strong collaboration between IR and oncology nurses within our institution to ensure patient safety.

Before scheduling IAC, an eye examination that includes a complete ophthalmoscopic examination, an ultrasound to determine tumor dimensions, and an electroretinogram are performed in a separate procedure under general anesthesia. An electroretinogram measures the electrical activity of retina in response to stimulation. Local treatment using cryotherapy (cold) and or laser (heat) is often required and administered by the ophthalmologist during each eye examination under anesthesia (EUA), beginning with the first course of chemotherapy. The local therapy given will depend on the tumor size and location (Rodriguez-Galindo et al., 2015). This local therapy is standard in the treatment of retinoblastoma (Rodriguez-Galindo et al., 2015). The need for local treatment is determined by the interdisciplinary medical team. Local treatment is used in combination with chemotherapy and appears to have a synergistic effect in treating retinoblastoma