Retinoblastoma: What’s new?

La-onsri Atchaneeyasakul, M.D.
Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Siriraj Med J 2007; 59: 144-145
E-journal: http://www.sirirajmedj.com

Retinoblastoma continues to be the most common primary intraocular malignancy in children. At Siriraj Hospital Mahidol University, we identify 12-15 new retinoblastoma patients each year. In the US, approximately 400 children are diagnosed with this disease every year. In the old days, most children with retinoblastoma died from metastatic diseases. Due to the improvement of medical care and public concern, retinoblastoma is becoming a less fearful disease.

It has been recognized that "leukocoria", or white pupil, is the major presenting sign of the disease. Unfortunately, by the time the parents or guardians were aware of this sign, the tumor has usually enlarged more than half the size of the eyeball and those eyes must be removed surgically. Therefore, early detection and proper diagnosis is the main key for saving the patient’s life and salvaging the eye.

Once the patient is diagnosed with retinoblastoma, the eye will be classified according to Reese-Ellsworth Classification for intraocular tumors into Group I to V. This new classification system was developed 43 years ago with the aim of predicting visual prognosis after treatment with surgery and external beam radiotherapy. Since then, there have been advances and modifications in the treatment modalities for the disease. This necessitated the development of other classification systems which may offer more accuracy in giving prognosis for salvaging the eye and signifying treatment options. One of the new classification systems for the disease that confines to the eye was the International Classification system created by several retinoblastoma centers in the US. This new staging system is based on the size and location of intraocular tumors and it is categorized into Group A to E. Group A disease, with small tumor(s) not occupying the fovea or optic disc, has the best prognosis for salvaging the eye and could be treated with local modalities such as cryotherapy or laser photocoagulation. In Group E disease, the tumor(s) extend more than one half size of the eyeball or involve the anterior segment of the eye. Those eyes are most likely to be enucleated with very limited chance of salvaging the eye.

Generally, retinoblastoma tumor cells are sensitive to radiotherapy and systemic chemotherapy. However, these two treatment modalities have not been used regularly as an initial therapy due to their serious adverse effects. Children with bilateral disease are prone to develop second malignant neoplasms especially when they receive external beam radiotherapy to the eye. Similarly, systemic chemotherapy may induce other types of malignancy later in life. During the past ten years, combined systemic chemotherapy with 2 to 4 drugs have been introduced as a primary treatment for Group C and D intraocular retinoblastoma. For Group C disease, the idea is to reduce the tumor size with systemic chemotherapy until it is small enough to be treated with local modalities. This is called “chemoreduction”. In Group D intraocular retinoblastoma, diffuse vitreous seeding is the characteristic. Normally, this eye would either be enucleated or treated with external beam radiotherapy. In order to avoid those treatments, there have been studies using combined systemic chemotherapy with the addition of cyclosporin A (CSA). Clinical efficacy of CSA has been attributed to multidrug resistance reversal activity. Moreover, “cryodisruption” is performed prior to each cycle of chemotherapy to break the blood-retinal barrier and increase chemotherapy levels within the tumors and the vitreous cavity. With the technique, some eyes in the Group D could be salvaged and radiotherapy might be avoided or delayed.

One of the downsides of cytotoxic chemotherapy is the lack of selectivity of the drugs, which extends their toxicity to normal tissues. This drives the researchers around the world to investigate alternative treatment methods. During the past decade, there have been several studies either in vitro and/or in vivo involving the new therapy for retinoblastoma. Some of those exciting researches have been suicide gene therapy and the use of antiangiogenic agents. “Suicide gene therapy” or “gene-directed enzyme prodrug therapy” is an innovative approach to enhance drug selectivity towards solid tumor cells. There are two steps involved including the delivery and expression of a gene encoding for a foreign enzyme into the tumor and the administration of a prodrug to the patient. The introduced foreign enzyme will activate the prodrug and release a cytotoxic drug which leads to tumor cell killing.

Two of the well-known systems of suicide gene therapy include herpes simplex virus thymidine kinase - gancyclovir (HSV-TK/GCV) therapy and cytosine deaminase - 5-fluorocytosine (CD/5-FC) therapy. As for HSV-TK/GCV combination, gancyclovir (GCV) is phosphorylated to GCV-monophosphate (GCV-MP) by HSV-TK. GCV-MP is then phosphorylated to GCV-biphosphate (GCV-BP) and GCV-triphosphate (GCV-TP) by the enzyme kinases within the tumor cells. GCV-TP then integrates into the host genome...
and causes DNA chain termination. This leads to apoptosis of the tumor cells. Recently, the feasibility and safety of HSV-TK/GCV gene therapy has been evaluated in a clinical trial for 8 children with intraocular retinoblastoma with active vitreous seeds refractory to standard therapies. The results showed resolution of the vitreous seeds with mild to moderate inflammation in the eyes. Although suicide gene therapy shows its potential as an alternative treatment for retinoblastoma and other solid tumors, several questions need to be answered and several techniques such as vector design, tumor targeting, and mechanisms of untransfected tumor cell killing need to be improved.

It has been known for a long time that “angiogenesis” or the growth of new blood vessels from preexisting vessels is one of the fundamental steps in cancer development. This concept is, without exception, applied to the expansion of retinoblastoma tumor within the eye. At present, a study on angiogenesis inhibitors is a groundbreaking field in cancer research. Among those agents with anti-angiogenic effect, bevacizumab (trade name Avastin®) which is a recombinant humanized monoclonal antibody against an isofrom of vascular endothelial growth factor, has been first approved by the US Food and Drug Administration for use as part of combination therapy for colorectal cancer. Recently, there have been studies, either in vitro and/or in vivo, on different agents with anti-angiogenic effect for the treatment of intraocular retinoblastoma. However, the results were controversial. Personally, the author had an experience working on tumstatin synthetic peptides which have the anti-angiogenic and tumor suppressor effects. Both in vitro and in vivo experiments demonstrated promising effect of tumstatin synthetic peptide residues 185-203 for suppressing retinoblastoma cell proliferation (manuscript in preparation). Further study using a large number of different retinoblastoma cell lines and different nonhuman primates is required in order to confirm the effectiveness of this agent.

Last but not least, preimplantation genetic diagnosis (PGD) has recently been investigated and used for families who have children with germinal retinoblastoma. The principle of this innovative technique includes a standard in vitro fertilization procedure and preselecting or transferring only mutation-free embryos back to the mother. Examples of other at-risk couples who received the benefit from PGD include familial adenomatous polyposis coli, von Hippel Lindau syndrome, Li-Fraumeni syndrome, neurofibromatosis type I and II, and familial posterior fossa brain tumor.

During the past century, a great deal of knowledge has been discovered for retinoblastoma, most of which has a significant impact on the line of treatment and prevention. It is important for those clinicians who take care of retinoblastoma patients to keep themselves up-to-date and are able to apply the state-of-the-art technology for the greatest benefit to the patients and their families.

REFERENCES