RETINOBLASTOMA

Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

RETINOBLASTOMA

Executive Summary

Retinoblastoma is the most frequent neoplasm of the eye in childhood, and represents 3% of all childhood malignancies. It is a cancer of the very young; two-thirds are diagnosed before 2 years of age, and 95% before 5 years. For these reasons, therapeutic approaches need to consider not only the cure of the disease but also the need to preserve vision with minimal long-term side effects. The average age-adjusted incidence rate of retinoblastoma in the United States and Europe is 2-5/10^6 children (approximately 1 in 14,000 – 18,000 live births). However, the incidence of retinoblastoma is not distributed equally around the world. It appears to be higher (6-10/10^6 children) in Africa, India, and among children of Native American descent in the North American continent. Whether these geographical variations are due to ethnic or socioeconomic factors is not well known. However, the fact that even in industrialized countries an increased incidence of retinoblastoma is associated with poverty and low levels of maternal education, suggests a role for the environment. Retinoblastoma presents in two distinct clinical forms: (1) A bilateral or multifocal, heritable form (25% of all cases), characterized by the presence of germ-line mutations of the RB1 gene; and (2) a unilateral or unifocal form (75% of all cases), 90% of which are non-hereditary. The most common presenting sign of retinoblastoma is leukocoria, and some patients may also present with strabismus. As the disease advances, patients present with buphthalmos, orbital, and metastatic disease. Therefore, early diagnosis, while the disease is still intra-ocular, is key and cancer control initiatives aimed at early recognition of signs of retinoblastoma have the potential of a great impact, both improving cure rates and minimizing the need for intensive treatments.

The treatment of retinoblastoma is multi-disciplinary, aims at saving life and preserving vision, and needs to be adapted to laterality and to the extent of disease (intra and extra-ocular). Intra-ocular disease is highly curable; more than 90% of patients survive. Early intraocular stages are candidates for ocular preservation; in such circumstances, treatment includes systemic or intra-arterial chemotherapy for cytoreduction, coupled with aggressive focal therapies such as thermotherapy, brachytherapy, and cryotherapy, and external-beam radiation therapy. Advanced intra-ocular disease requires enucleation; adjuvant chemotherapy and radiation therapy may be indicated in a subset of patients with high-risk pathology. Patients with extra-ocular disease have a much worse outcome. If the disease is limited to the orbit, a combination of chemotherapy, surgery, and radiation therapy may be effective and cure 50-70% of patients. The presence of extra-orbital (metastatic) disease carries a dismal prognosis; less than 20% of patients can be cured with standard treatments. However, if metastases do not include the CNS, the use of consolidation treatment with high-dose chemotherapy and autologous hematopoietic stem cell rescue may cure 50-70% of patients. Patients with bilateral disease and a germline mutation are at high-risk for second malignancies; this risk increases with the use of radiation therapy.
Public Health Relevance

Epidemiology summary The estimated incidence of retinoblastoma is 1 in 16,000-18,000 births annually with between 7000 and 8000 new cases per year worldwide. The annual incidence is 3.5 per million children younger than 15 and 11.8 per million children younger than 5 years of age. While survival rates in the United States are nearly 100%, they are much lower in developing nations. Survival rates range from 80-89% in more developed Latin American countries to as low as 20-46% in certain African countries. More than 90% of children with retinoblastoma live in low and middle-income countries (LMIC), but those countries have 90% of the cases presenting with metastatic disease, and virtually all the cases that abandon therapy. As a result of lower survival rates, there are an estimated 3000 to 4000 deaths annually due to retinoblastoma. The discrepancies in survival rates emphasize the potential to reduce retinoblastoma-caused through timely diagnosis and proper treatment.

Additional Details Regarding Burden of Disease

1. Importance of early detection: The successful management of retinoblastoma depends on the ability to detect the disease while it is still intra-ocular. Disease stage correlates with delay in diagnosis; growth and invasion occur as a sequence of events, and extra retinal extension occurs only once the tumor has reached large intra-ocular dimensions. Although retinoblastoma is very curable when diagnosed early and treated appropriately, the prognosis is dismal when the basic elements in diagnosis and treatment are lacking. While in high-income countries (HIC) retinoblastoma typically presents intraocularly, in LMIC, 60-90% of children present with extra-ocular disease. Lack of education, limited access to health care, and complex and deficient socio-economic environments result in delayed and under diagnosis in LMIC. However, the magnitude of the problem is difficult to ascertain given the paucity of population-based cancer registries. Retinoblastoma educational and public awareness campaigns have been shown to increase referrals, decrease rates of advanced disease, and improve outcomes in LMIC. However, the level of awareness of the first contact health provider in identifying the problem and making the appropriate referrals is critical; the lack of knowledge by first contact physicians has been shown to be a significant barrier, thus highlighting the importance of targeting primary healthcare providers.

2. Cost effectiveness of developing public health initiatives in retinoblastoma: Early diagnosis is key in retinoblastoma. Failure of public awareness and deficiencies in education among first contact healthcare providers represent major barriers to early diagnosis and result in the high incidence of metastatic disease and mortality rates in LMIC. In HIC, children with retinoblastoma are usually diagnosed with advanced intra-ocular disease; by the time leukocoria is obvious, the tumor is usually filling more than 50% of the eye globe, making ocular salvage a major challenge. Most eyes with unilateral disease are enucleated, and children with bilateral retinoblastoma undergo aggressive treatments. The tremendous impact that modern ocular-preservation treatments have on these young children and their families should not be underestimated. Thus, both in HIC and LMIC, the diagnosis of a child with retinoblastoma unveils a deficiency in early diagnosis, just in different magnitude. Since retinoblastoma is a cancer of the infant and young child, initiatives aiming at early recognition during standard health supervision
visits and immunizations should facilitate diagnosis, decrease the disease and treatment burden, and increase survival. 

Requirements for diagnosis, treatment, and monitoring

**Diagnostics:** The diagnosis of intra-ocular retinoblastoma does not require pathologic confirmation; treatment decisions (eye salvage vs. enucleation) are usually made on best clinical judgment by an experienced ophthalmologist. An examination under anesthesia with a maximally dilated pupil and scleral indentation is required to examine the entire retina. A very detailed documentation of the number, location and size of tumors, the presence of retinal detachment and sub-retinal fluid and the presence of vitreous and sub-retinal seeds must be performed. The evaluation of the enucleated eye includes basic immunohistochemistry; retinoblastoma has a very distinct histology and no specific markers are necessary. Evaluation of disease extension into the anterior chamber, choroid, sclera, and optic nerve is required for proper treatment considerations.

Growth and invasion of retinoblastoma occur as a sequence of events, and extra-retinal and extra-ocular extension occur only once the tumor has reached large intra-ocular dimensions. As part of this process, retinoblastoma extends into the ocular coats (choroid and sclera) and the optic nerve. Extra-ocular disease is the next step in this progression. Loco-regional dissemination occurs by direct extension through the sclera into the orbital contents and pre-auricular lymph nodes, and extra-orbital disease manifests as intracranial dissemination and hematogenous metastases, usually to bones, bone marrow and liver. Therefore, early diagnosis while the disease is intra-ocular is of utmost importance; education of primary care providers and community health workers is essential.

**Testing:** Additional imaging studies that aid in the diagnosis and staging include bi-dimensional ocular ultrasound, computerized tomography and magnetic resonance imaging. These imaging studies are particularly important to evaluate extra-ocular extension and to differentiate retinoblastoma from other causes of leukocoria. For patients with evidence of extra-ocular disease or with high-risk pathology in the enucleated eye, evaluation for the presence of metastatic disease also needs to be considered, and additional staging procedures, including bone scintigraphy, bone marrow aspirates and biopsies, and lumbar puncture, must be performed.

**Administration and Care of Patients:** Administration of chemotherapy requires intravenous infusion capacity and regular access to clinical care. For patients with intra-ocular disease, chemotherapy is used either as cytoreductive therapy for eye-salvage or in the adjuvant setting after enucleation for patients with advanced disease who have high-risk pathology. The VCE regimen is used in both settings; chemotherapy can usually be given in the outpatient setting and toxicity is moderate. Patients require standard hydration and anti-emetics. Infusion of vincristine requires close monitoring to prevent extravasation. Myelosuppression is mild to moderate; transfusional support is not always required; and while growth factor support is recommended, it is not always necessary. In HIC, ocular salvage treatment for patients with early intra-ocular disease may include direct infusion of chemotherapy (usually melphalan) into the ophthalmic
artery of the affected eye. This requires a sophisticated interventional radiology setting, usually only available in HIC. Toxicity of this approach is quite low.

Treatment for patients with advanced (extra-ocular) disease is more intensive. Cisplatin-based regimens are often used during the induction phase. Administration of chemotherapy is usually in the inpatient setting; aggressive hydration and anti-emetic therapy are needed, and renal function and electrolyte balance need to be monitored closely. Toxicity is higher; most patients require transfusional and growth factor support. The less toxic VCE regimen described above can be used for patients with disease limited to the orbit in LMIC. For patients with extra-ocular disease, consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue is recommended. However, this approach is only available in high-income countries.

Radiation therapy is indicated in patients with bilateral disease in the setting of an ocular salvage plan, and in all patients with extra-ocular disease.

Long-term follow-up for survivors of retinoblastoma requires close coordination with primary care, the school system and the social supporting structures. Visual impairment and difficult integration into school and society is a constant in retinoblastoma survivors, and survivorship programs must coordinate initiatives with programs aimed at those visually disabled. But more importantly, survivors of bilateral or hereditary disease have a significantly increased risk of developing second malignancies. The cumulative incidence of a second cancer is in excess of 30 to 40%, and this risk is particularly high in those patients who received radiation therapy. Almost any neoplasm has been described in survivors of retinoblastoma. The most common second tumor is osteosarcoma, both inside and outside the radiation field, and soft tissue sarcomas and melanomas are second in frequency.

**Overview of Regimens**

The following table includes basic information on administration and dosing for the regimens for intraocular and extraocular disease, and excludes ancillary medications pertaining to the management of side effects.

**Essential Regimen**

Indicated for intra-ocular disease, either in the eye salvage setting or after enucleation for patients with high-risk pathology; also effective in patients with extra-ocular disease limited to the orbit.

**VCE: 6 cycles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Schedule</th>
<th>&lt; 36 months</th>
<th>≥ 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vincristine</strong></td>
<td>Intravenous infusion (push)</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 36 months</td>
<td>0.05 mg/kg</td>
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<tr>
<td></td>
<td></td>
<td>≥ 36 months</td>
<td>1.5 mg/m²</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td>Intravenous infusion (1 hour)</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 36 months</td>
<td>18.6 mg/kg</td>
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<tr>
<td></td>
<td></td>
<td>≥ 36 months</td>
<td>560 mg/m²</td>
</tr>
<tr>
<td><strong>Etoposide</strong></td>
<td>Intravenous infusion (1 hour)</td>
<td>Days 1, 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 36 months</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 36 months</td>
<td>150 mg/m²</td>
</tr>
</tbody>
</table>

* Max dose = 2 mg
Review of Benefits and Harms

Survival Benefits

Retinoblastoma is a highly curable disease when diagnosed early. For patients with unilateral intra-ocular disease, enucleation may be curative, although approximately 20-30% of those patients may have high-risk pathology and require adjuvant chemotherapy. The long-term outcome of this group of patients is excellent; more than 80% survive. The outcome for patients with unilateral disease that has been enucleated is excellent, with good functional results and minimal long-term effects. The treatment of patients with bilateral retinoblastoma treated in state of the art treatment centers and on whom ocular salvage is intended incorporates up-front chemotherapy, which is intended to achieve maximum chemo-reduction of the intra-ocular tumor burden early in the treatment, followed by aggressive focal therapies. This approach has resulted in an increase in the eye salvage rates and in a decrease (and delay) in the use of radiation therapy. For patients with advanced intra-ocular tumors, ocular salvage rates can be above 60-70%, with survival rates in excess of 90%. Intra-arterial chemotherapy delivery can result in better ocular salvage rates, although this approach is limited to state of the art treatment centers. Patients presenting with orbital disease benefit from more intensive systemic therapy and orbital radiotherapy; using this approach 50-80% of the patients can be cured. Patients with metastatic retinoblastoma without CNS disease can be cured using high-dose, marrow-ablative chemotherapy and autologous hematopoietic stem cell rescue; using this approach, up to 50% of patients may be cured. Intracranial dissemination of retinoblastoma carries a dismal prognosis, and while therapeutic intensification with high-dose, marrow ablative chemotherapy and autologous hematopoietic stem cell rescue has been explored, its role is not yet clear.

Harms and Toxicity Considerations

Vincristine commonly causes neurotoxicity, including sensory and motor neuropathies, which is typically dose-related. Neurotoxicity is usually reversible, though recovery may be gradual and may be incomplete. Vincristine also causes constipation which can be severe; patients should receive prophylaxis.

The most frequent dose-limiting toxicity for etoposide is myelosuppression, primarily leukopenia which can be grade 3-4 in >10% of patients. A small percentage (up to 2%) of patients receiving intravenous etoposide experience hypersensitivity reactions, which may include angioedema, bronchospasm, and/or chest discomfort. Etoposide also causes reversible alopecia in up to 60% of patients. The use of etoposide has been associated with a small but increased risk of second cancers.

Platinum agents including cisplatin and carboplatin cause myelosuppression with dose-limiting thrombocytopenia, and also can cause ototoxicity and asthenia. Nausea and vomiting occur in almost all patients treated with cisplatin and carboplatin and are often severe, necessitating the use of anti-emetic medications. Renal toxicity caused by cisplatin can be significant and may
result in electrolyte abnormalities. Intravenous hydration both before and after administering cisplatin is necessary to reduce the incidence of renal toxicity.24

**Cyclophosphamide** can cause bladder toxicity, patients require additional hydration (>2L/m² daily) and frequent voiding in order to reduce the risk of hemorrhagic cystitis. It also commonly causes alopecia, mucositis, stomatitis, and may result in infertility.25

Pediatric patients treated for retinoblastoma have a significant risk of developing secondary malignancies, risk may be as high as 35% and is markedly increased in patients receiving radiation, particularly radiation at a very young age.26

**Systematic Reviews**


**Abstract**: Treatment of retinoblastoma must be individualized. Most patients with unilateral, non-metastatic retinoblastoma can be cured with enucleation alone. In patients with histologic risk factors, adjuvant chemotherapy is recommended, with the addition of orbital radiation for patients with trans-scleral involvement or tumor present at the level of the cut end of the optic nerve. Patients with metastases require intensive chemotherapy and consolidation with autologous hematopoietic stem cell rescue. Patients with bilateral or multifocal disease represent a major challenge. Cure of the disease is the first priority, but the therapeutic approach also has to consider eye and vision preservation. The approach is conservative, and only eyes with very advanced disease are enucleated upfront. Patients are treated with chemotherapy and intensive focal treatments, with the aim of delaying or avoiding radiation therapy and enucleation. For patients with early intra-ocular stage (Reese-Ellsworth groups I-III and International Groups A-B), the two-drug combination of vincristine and carboplatin is recommended. Patients with more advanced intra-ocular disease (Reese-Ellsworth groups IV-V and International Groups C-D) require more intensive chemotherapy. Standard of care for these patients incorporates etoposide into the regimen. Effective agents with good intra-ocular penetration, such as topotecan, are being investigated. Because most failures are secondary to progression of the vitreous seeds, subconjunctival carboplatin is added in cases with poor response of the vitreous tumors. Patients must be monitored very closely, with examinations under anesthesia every 4 to 6 weeks, and focal treatments are applied during the procedure. These include cryotherapy for small anterior tumors, thermotherapy and laser photocoagulation for small posterior tumors, and brachytherapy for larger tumors. New treatment approaches under development include the refinement of peri-ocular chemotherapy administration using slow-release devices, the use of suicide gene therapy with local delivery of the herpes simplex tyrosine kinase gene (followed by systemic administration of ganciclovir), and the development of small molecule inhibitors of the MDMX-p53 interaction.

Abstract: Survival of retinoblastoma is >90% in developed countries but there are significant differences with developing countries in stage at presentation, available treatment options, family compliance, and survival. In low-income countries (LICs), children present with advanced disease, and the reasons are socioeconomic and cultural. In middle-income countries (MICs), survival rates are better (>70%), but there is a high prevalence of microscopically disseminated extra-ocular disease. Programs for eye preservation have been developed, but toxicity-related mortality is higher. Although effective treatment of microscopic extra-ocular disease improved the outcome, worldwide survival will be increased only by earlier diagnosis and better treatment adherence.


Abstract: Purpose of review: The management of retinoblastoma is complex and involves strategically chosen methods of enucleation, radiotherapy, chemotherapy, laser photocoagulation, thermotherapy, and cryotherapy. Chemotherapy has become the most common eye-sparing modality. There are four routes of delivery of chemotherapy for retinoblastoma, including intravenous, intra-arterial, periocular, and intravitreal techniques. The purpose of this review is to discuss the current rationale for each method and the anticipated outcomes. Recent findings: The diagnosis of retinoblastoma should be clinically established prior to embarking on a chemotherapy protocol. There are over 25 conditions that can closely simulate retinoblastoma in a young child. In addition, enucleation is an acceptable method for management, particularly with advanced retinoblastoma. Intravenous chemotherapy is generally used for germline mutation (bilateral, familial) retinoblastoma with excellent tumor control for groups A, B, and C and intermediate control for group D eyes. Intra-arterial chemotherapy is used as primary therapy in selected cases for non-germline mutation (unilateral) retinoblastoma with excellent control, and also used as secondary therapy for recurrent solid retinoblastoma, sub-retinal seeds, and vitreous seeds. Peri-ocular chemotherapy is employed to boost local chemotherapy dose in advanced bilateral groups D and E eyes or for localized recurrences. Intra-vitreal chemotherapy is used for recurrent vitreous seeds from retinoblastoma. Patients at high risk for metastases should receive intravenous chemotherapy. Summary: Chemotherapy is effective for retinoblastoma and the targeted treatment route depends on the clinical features and anticipated outcomes.

Additional literature
Recommendations

The reviewers recommend the incorporation of retinoblastoma cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that cisplatin, carboplatin, and etoposide be added for pediatric indications to the core Essential Medicines List.

Medicines proposed for Section 8.2 of the Child EML

Cisplatin
Carboplatin
Etoposide
References

22. Castells MC, Matulonis UA. Infusion reactions to systemic chemotherapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.