Retinoblastoma – EMLc

The application sought the addition of cisplatin, carboplatin and etoposide to the core list of Essential Medicines for Children for the treatment of retinoblastoma. The application also sought endorsement for the use of vincristine (already on the complementary list of the EMLc for other indications) for retinoblastoma.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

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 of cases are diagnosed before 2 years of age and 95% before 5 years *(1)*. For these reasons, therapeutic approaches need to consider not only 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 Europe and the United States is 2–5 per one million children. Incidence of retinoblastoma is not evenly distributed around the world and appears to be higher in Africa, India, and among children of Native American descent in the North American continent *(2)*. Whether these geographical variations are due to ethnic or socioeconomic factors is unclear but 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 *(3, 4)*.

Retinoblastoma presents in two distinct clinical forms:

- bilateral (both eyes) or multifocal (one eye with multiple distinctly separate tumour foci), heritable form (25% of all cases), characterized by the presence of germline mutations of the *RB1* gene and predisposition for developing second cancers later in life; and
- unifocal (affecting one retinal cell only and unilateral disease) 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 exophthalmos and metastatic disease. Early diagnosis, while the disease is still intraocular, is therefore key, and cancer control initiatives aimed at early recognition of signs of retinoblastoma have the potential for enormous impact, both improving cure rates and minimizing the need for intensive treatments.

The treatment of retinoblastoma is multidisciplinary, aims to save life and preserve vision, and needs to be adapted to laterality and to the extent of disease (intra and extraocular). Intraocular disease is highly curable: more than 90% of patients survive. Early intraocular stages are candidates for ocular preservation; treatment includes systemic neoadjuvant chemotherapy for chemoreduction, coupled with aggressive focal therapies such as thermotherapy, brachytherapy, cryotherapy and external-beam radiation therapy.

Advanced intraocular disease requires enucleation; adjuvant chemotherapy and radiation therapy may be indicated in a subset of patients with high risk pathology. Outcome is much worse in patients with extraocular disease. 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 extraorbital (metastatic) disease carries a poor prognosis; less than 20% of patients are cured with standard treatments. However, if metastases do not include the central nervous system, the use of consolidation treatment with high-dose chemotherapy and autologous haematopoietic 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 *(5)*. In the United States, the mean age-adjusted incidence is 11.8 per million children younger than 5 years of age *(6)*. While survival rates in the United States are nearly 100%, they are much lower in developing nations, ranging 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 (LMICs), but those countries have 90% of the cases presenting with metastatic disease and almost all the cases that abandon therapy *(7)*. As a result of lower survival rates, there are an estimated 3000–4000 deaths annually due to retinoblastoma *(8)*. The discrepancies in survival rates emphasize the potential for reducing retinoblastoma-related deaths through timely diagnosis and proper treatment.

Additional details regarding burden of disease

Importance of early detection

Successful management of retinoblastoma depends on the ability to detect the disease while it is still intraocular. Disease stage correlates with delay in diagnosis; growth and invasion occur as a sequence of events, and extraretinal extension occurs only once the tumour has reached large intraocular dimensions. Although retinoblastoma is very curable when diagnosed early and treated appropriately, the prognosis is dismal when the basic elements of diagnosis and treatment are lacking. In high-income countries, retinoblastoma typically presents intraocularly, while 60–90% of cases in LMICs present with extraocular disease. Lack of education, limited access to health care, and complex and deficient socioeconomic environments are associated with delayed diagnosis or under-diagnosis in LMICs. However, the magnitude of the problem is difficult to ascertain given the paucity of population-based cancer registries. Even in high-income countries, children with retinoblastoma are not always diagnosed with early-stage intraocular disease; by the time leukocoria is obvious, the tumour 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 *(9)*.

Importance of public health initiatives in retinoblastoma

Educational and public awareness campaigns have been shown to increase referrals for retinoblastoma, reduce rates of advanced disease, and improve outcomes in LMICs *(10, 11)*. The level of awareness of the first-contact health provider in identifying the problem and making the appropriate referrals is critical. Lack of knowledge among first-contact physicians has been shown to be a significant barrier to early diagnosis and to result in high incidence of metastatic disease, thus highlighting the importance of targeting primary health-care providers *(12)*. Since retinoblastoma is a cancer of infants and young children, initiatives aimed at early recognition during standard health supervision and immunization visits should facilitate diagnosis, reduce the disease and treatment burden, and increase survival *(13)*. Published results from several countries reveal that coordinated efforts in primary and secondary care settings and development of centres of excellence for conservative management of retinoblastoma were associated with improvements in 5-year survival rates, number of patients presenting with extraocular disease, and median age at diagnosis *(14-16)*.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Diagnosis of intraocular retinoblastoma does not require pathological confirmation; an examination under anaesthesia with a maximally dilated pupil and scleral indentation is required to inspect the entire retina. Highly detailed documentation of the number, location and size of tumours, the presence of retinal detachment and subretinal fluid and of vitreous and subretinal seeds is essential. Evaluation of the enucleated eye includes basic histology since 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.

Loco-regional dissemination occurs by direct extension through the sclera into the orbital contents and pre-auricular lymph nodes, and extraorbital disease manifests as intracranial dissemination and haematogenous metastases, usually to bones, bone marrow and liver.

Testing

Additional imaging studies that aid in the diagnosis and staging include two-dimensional ocular ultrasound, computerized tomography and magnetic resonance imaging. These

imaging studies are particularly important for evaluating extraocular extension and differentiating retinoblastoma from other causes of leukocoria. For patients with evidence of extraocular 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 *(17)*.

Administration and care of patients

Treatment decisions (eye salvage versus enucleation) are usually made on best clinical judgement by an experienced ophthalmologist.

Administration of chemotherapy requires intravenous infusion capacity and regular patient access to clinical care. For patients with intraocular disease, chemotherapy is used as either neoadjuvant or chemoreductive therapy for ocular salvage and, in the adjuvant setting, after enucleation for patients with advanced disease who are at high risk for recurrence. The VCE regimen (vincristine, carboplatin, etoposide) is used in both settings. Chemotherapy can usually be given in the outpatient setting and toxicity is moderate; patients require standard hydration and antiemetics. 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 high-income countries, ocular salvage treatment for patients with early intraocular disease may include direct infusion of chemotherapy (usually melphalan) into the ophthalmic artery of the affected eye, which requires sophisticated interventional radiology. The toxicity of this approach is quite low.

Treatment for patients with advanced (extraocular) 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 antiemetic therapy are needed, and renal function and electrolyte balance need to be monitored closely. Toxicity is high; most patients require transfusional and growth factor support. The less toxic VCE regimen described above can be used in LMICs for patients whose disease is limited to the orbit. For patients with extraocular disease, consolidation with high-dose chemotherapy and autologous haematopoietic stem-cell rescue is recommended, but this approach is available only 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 extraocular disease.

Long-term follow-up for survivors of retinoblastoma requires close coordination with primary care, the school system and supporting social infrastructure. Visual impairment and difficult integration into school and society are constants in retinoblastoma survivors, and survivorship programmes must coordinate initiatives with programmes aimed at visually disabled individuals. 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 30–40%, and this risk is particularly high in patients who receive radiation therapy *(18)*. Almost every neoplasm has been described in survivors of retinoblastoma; the most common second tumour is osteosarcoma, both inside and outside the radiation field, and soft tissue sarcomas and melanomas are the second most common.

Overview of regimens

Essential regimen

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

- **VCE (6 cycles)**

–	vincristine[1] IV infusion (push) on day 1	< 36 months	0.05 mg/kg
		≥ 36 months	1.5 mg/m^2
–	carboplatin IV infusion (1 hour) on day 1	< 36 months	18.6 mg/kg
		≥ 36 months	560 mg/m^2
–	etoposide IV infusion (1 hour) on days 1 and 2	< 36 months	5 mg/kg
		≥ 36 months	150 mg/m^2

Ancillary medications pertaining to the management of side-effects have not been included.

Review of benefits and harms

Survival benefits

The aims of treatment are to ensure survival, preserve the eye and salvage useful vision. Historically, enucleation has been the standard treatment for patients with early-stage unilateral intraocular disease. However, approximately 20–30% of patients treated by enucleation may have high-risk pathology and require adjuvant chemotherapy and external beam radiation therapy. The latter is associated with the risk of developing radiation-induced secondary tumours and other long-term complications, including cataracts, dry eye and facial growth asymmetry. This has led to an increasing trend towards the use of focal conservative treatments and chemotherapy, where possible.

Some studies have shown that the outcomes for patients with unilateral disease that has been enucleated are positive, with good functional results (e.g. large majority of children with normal vision in at least one eye) and minimal long-term effects (e.g. large majority normal in growth and health, average mental and motor development scores in normal range) *(19)*.

[1] Maximum dose = 2 mg.

Retrospective and prospective controlled studies have investigated the efficacy of post-enucleation adjunctive chemotherapy using VCE in preventing metastasis in patients with high-risk retinoblastoma *(20, 21)*. In one study involving 80 patients, post-enucleation adjuvant VCE was administered to 25 patients with high-risk retinoblastoma, while another 21 patients received the older regimen of vincristine, doxorubicin and cyclophosphamide *(20)*. Median follow-up was almost 5 years, after which the rates of metastasis were 4% and 24% in the adjuvant therapy and no adjuvant therapy treatment groups, respectively. The authors concluded that adjuvant therapy was responsible for significantly reducing the risk of metastases in patients with retinoblastoma with high-risk characteristics. In a second study of 52 eyes (in 51 patients), treatment with VCE chemotherapy resulted in a 0% incidence (95% CI 0%: 14%) of metastasis after a median follow-up of 5 years *(21)*. No deaths were recorded. The authors concluded that VCE was effective as post-enucleation chemotherapy in high-risk retinoblastoma patients in terms of preventing systemic metastases, and was thus likely to improve survival.

A systematic review exploring the findings of studies comparing chemotherapy with no chemotherapy, or differences between chemotherapy regimens, was unable to draw meaningful conclusions because of the small number of patients in the studies, the lack of information about the treatment received by the comparison group, and the lack of consideration of potential confounding factors *(22)*. The most commonly used chemotherapeutic drugs are vincristine, etoposide and carboplatin, with or without the addition of ciclosporin. The number of cycles varies from two to more than eight in different treatment centres, although this is related to the stage of disease *(23)*, with longer courses typically required to treat systemic retinoblastoma.

The treatment in tertiary care centres of patients with bilateral retinoblastoma, in whom ocular salvage is the aim, incorporates initial chemotherapy, intended to achieve maximum chemoreduction of the intraocular tumour burden early in the treatment, followed by aggressive focal therapies. This approach has resulted in an increase in eye salvage rates and in a decrease (and delay) in the use of radiation therapy. For patients with advanced intraocular tumours, ocular salvage rates can exceed 60–70%, with survival rates in excess of 90% *(24)*. Intra-arterial chemotherapy delivery can result in better ocular salvage rates, although this approach is limited to advanced tertiary care centres *(25-28)*. Patients presenting with orbital disease benefit from more intensive systemic therapy and orbital radiotherapy; using this approach 50–80% of patients can be cured *(29)*. Up to 50% of patients with metastatic retinoblastoma without central nervous system disease can be cured using high-dose, marrow-ablative chemotherapy and autologous haematopoietic stem-cell rescue *(30)*. Intracranial dissemination of retinoblastoma carries a poor prognosis; the role of therapeutic intensification with high-dose, marrow ablative chemotherapy and autologous haematopoietic stem cell rescue has been explored but remains unclear *(31)*.

Harms and toxicity considerations

Vincristine commonly causes neurotoxicity – including sensory and motor neuropathies – which is typically dose-related. Neurotoxicity is usually reversible, although recovery may be gradual and possibly incomplete. Vincristine also causes constipation which can be severe; patients should receive prophylaxis *(32)*.

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 *(33)*. Etoposide also causes reversible alopecia in up to 60% of patients *(34)*. The use of etoposide has been associated with a small but increased risk of second cancers.

Platinum-based agents, including cisplatin and carboplatin, cause myelosuppression with dose-limiting thrombocytopenia and can also 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 antiemetic medications. Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration both before and after administration of cisplatin is necessary to reduce the incidence of renal toxicity *(35)*.

Cyclophosphamide can cause bladder toxicity, and patients require additional hydration (>2 L/m^2 daily) and frequent voiding in order to reduce the risk of haemorrhagic cystitis. It also commonly causes alopecia, mucositis and stomatitis, and may result in infertility *(36)*.

Paediatric patients treated for retinoblastoma have a significant risk of developing secondary malignancies; the risk may be as high as 35% and is markedly increased in patients receiving radiation, particularly at a very young age *(37)*.

Overall, only a limited number of studies reported data on adverse events, and a small proportion of patients were monitored to assess the impact of treatment on children's general development, including cosmetic complications and visual acuity. Data on adverse events and emotional and psychological development have apparently been only rarely gathered, which limits the quality of evidence.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended addition of vincristine, carboplatin, cisplatin and etoposide to the Model List of Essential Medicines for Children for the treatment of retinoblastoma. The Committee noted that vincristine is currently listed on the EMLc for use in the treatment of other cancers.

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