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CLINICAL PRACTICE GUIDELINES
SIOP-PODC Recommendations for Graduated-Intensity Treatment of Retinoblastoma in Developing Countries

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Retinoblastoma remains incurable in many regions of the world. The major obstacles to cure are delayed diagnosis, poor treatment compliance, and lack of evidence-based recommendations for clinical management. Although enucleation is curative for intraocular disease, in developing countries retinoblastoma is often diagnosed after the disease has disseminated beyond the eye. A SIOP-PODC committee generated guidelines for the clinical management of retinoblastoma in developing countries and developed a classification system based on the resources available in those settings. Recommendations are provided for staging and treatment of unilateral and bilateral retinoblastoma and counseling of families for whom compliance is an issue. Pediatr Blood Cancer 2013;60:719–727.
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INTRODUCTION

Retinoblastoma is highly curable in developed countries; however, most children with retinoblastoma in developing countries die as a result of late diagnosis and poor treatment compliance, which leads to extraocular dissemination and metastasis [1]. Since it is estimated that about 2/3 of the population in the pediatric age live in developing countries, there may be more children dying of retinoblastoma than those surviving worldwide [2]. In developed countries, patients with unilateral disease can be cured by enucleation of the affected eye, whereas those with bilateral disease undergo eye-conserving therapies in at least on one eye. Enucleation is a relatively simple surgical procedure that requires no special facility or equipment and is potentially available in centers with limited resources [3]. However, even children who could be cured by enucleation, present with substantial challenges in developing countries. Their families do not always approve of enucleation [4], and the prevalence of patients presenting with invasion to critical eye structures (i.e., postlaminar optic nerve, sclera, or choroid) is high [5], so adjuvant therapy after enucleation is usually needed to prevent extraocular relapse.

Accurate risk assignment of patients with retinoblastoma requires standardized, expert evaluation of the pathologic features of the enucleated eye. This expertise is seldom available in less-developed countries. Thus, treatment decisions may be inaccurate in that setting. In addition, patients who present with overt extraocular disease are not candidates for enucleation, and the likelihood of cure is only realistic in those cases in which the tumor has disseminated to the orbit only. Children with metastatic retinoblastoma are seldom cured by conventional therapy [6].

Controversies are exist for conservative therapies. In developed countries, external-beam radiotherapy (EBRT) was the classic, initial effective conservative therapy for retinoblastoma. The use of radiation is associated with secondary malignancies, which are often fatal [7]. Therefore, EBRT has been virtually replaced by chemotherapy combined with local therapies (e.g., cryotherapy, laser therapy, etc.) aimed at preventing secondary malignancies. [7] Unfortunately, local treatments require a sophisticated setting and intense use of qualified staff members who may not be available in many developing countries [8]. In addition, localized approaches are less effective for treating more advanced disease. In such cases, radiotherapy is still needed, and enucleation may be ultimately required [9]. Local therapies have not increased the risk of extraocular dissemination in developed countries when used by experienced teams [10], but the situation may be different in developing countries. Conservative therapy is simply not an option in many countries because advanced disease is present at diagnosis, the technology and/or agents are not available, or follow-up is inadequate.

DEVELOPMENT OF RETINOBLASTOMA TREATMENT GUIDELINES

The literature on managing extraocular retinoblastoma is limited, so the evidence is weak in comparison to information available on treating other pediatric malignancies. For this report we used the National Cancer Institute levels of evidence [11]. We selected references from each setting and extrapolated those from other settings when no available reference was found. Thus, in

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cases with no published evidence, we assigned a level of evidence 4, based on recommendations of experts of this committee.

To develop these guidelines, an international group of retinoblastoma experts held teleconferences using the www.cure4kids.org website. Because retinoblastoma is associated with unique clinical management challenges in developing countries, the committee's proposal was presented at the regional SIOP Africa and Asia meetings in 2012. Issues were further discussed with local healthcare professionals and representatives from parental groups in attendance; treating children whose families do not consent to therapy was a main focus of those discussions. This consensus document includes representative cooperative groups (such as AHOPCA from Central America, RetMex from Mexico, and GALOP from South America) and international organizations (e.g., INCTR) that lead retinoblastoma protocols or programs.

As presented by Hunger and Howard [12] for the management of acute lymphoblastic leukemia, we propose recommendations for three settings with different resource availability for the management of retinoblastoma (Table I). Countries of low income (setting 1) have the fewest available resources and minimal technology (e.g., low-dose chemotherapy and minimal imaging, ophthalmologic, and pathology services). Lower-middle income (setting 2) countries have some basic resources (e.g., moderate-dose chemotherapy, some ophthalmological therapies). Upper-middle income (setting 3) countries have more modern resources and technologies (e.g., MRI, high-dose chemotherapy, highly specialized ophthalmological, and pathology services), but the availability of these features may be limited to larger centers. Some retinoblastoma-specific issues must also be considered, such as the type of facility where treatment is delivered (eye hospital, pediatric hospital, or cancer center), as this variable also influences the final recommendation (Table II).

In a given country, a center may have features of more than one setting. Because retinoblastoma is a rare malignancy, the care of patients with this disease should be centralized to referral centers that treat at least 5–10 patients with newly diagnosed disease per year [13]. Care provided by multiple specialists, including ophthalmologists, pediatric oncologists, anesthesiologists, psychologists, nurses, social workers, pathologists, radiation oncologists, imaging specialists, and others, working as a multidisciplinary team is essential for achieving optimal results in retinoblastoma [14]. The primary healthcare provider for children with retinoblastoma is typically an ophthalmologist. Therefore, a close relationship between the ophthalmologist and pediatric oncology team is essential.

TABLE I. Proposed System for Categorizing Retinoblastoma Treatment Settings in Developing Countries

Resource availability	Setting 1 (low-income)	Setting 2 (lower–middle income)	Setting 3 (upper–middle income)
Imaging	Not available or CT only	CT and occasionally MRI	MRI
Oncology treatment	Low-dose chemotherapy, Cobalt RT	Moderate-dose chemotherapy, Cobalt RT linear accelerator RT[a]	Moderate- and high-dose chemotherapy autologous hematopoietic stem cell rescue linear accelerator and 3D RT
Ophthalmologic treatment	Minimal	Cryotherapy, laser therapy, EBRT	Cryotherapy, laser-TTT, plaque oblation, EBRT (3D, IMRT), digital camera for funduscopy, Intra-arterial chemotherapy[a]
Pathology assessment	Minimal, low specialty, diagnosis confirmation	Low specialty, limited risk assessment	High-quality specialty, accurate risk assessment
Genetic testing	Not available	Not available	Limited availability, usually low resolution
Criteria for reclassification of setting	Ophthalmologist with training in conservative therapy Availability of laser therapy, cryotherapy, and RT Pathology assessment capable of accurate disease staging	Increased availability of localized therapies (laser-TTT, cryotherapy, and plaque ablation) <5% mortality related to toxicity of intensive chemotherapy regimen Second-line therapies for intraocular and extraocular relapse Highly specialized pathologic assessment capable of accurately stratifying patients to treatment	

CT, computed tomography; EBRT, external-beam radiation therapy; MRI, magnetic resonance imaging; RT, radiotherapy. [a]Limited availability.

AVAILABILITY OF SERVICES

The availability of services in developing countries guides the choice of treatment, so it is essential to identify the local facilities in which to either establish a new retinoblastoma program or optimize an existing one (Table II). Minimal requirements to for curative treatment of retinoblastoma include a dedicated ophthalmologist with adequate skill in eye enucleation in young children, the presence of a general pediatrician or pediatric oncologist and nursing staff familiar with chemotherapy administration and management of its side effect, supportive and palliative care, safe pediatric anesthesiology, availability of essential chemotherapy agents (cyclophosphamide, vincristine and doxorubicin [15,16], or preferably carboplatin and etoposide), and a

TABLE II. Resources Typically Available at Various Centers in Developing Countries

Resource	Eye hospital	Children's hospital	Cancer center
Chemotherapy support	Below standard	Standard, pediatric ICU	Standard, pediatric ICU may not be available
Local ophthalmic therapy	Usually good	Variable, limited availability	Variable, limited availability
Radiotherapy	Not available	Variable, limited availability	Available, but pediatric expertise may be limited
Palliative care	Not available	Usually available	Available, but pediatric expertise may be limited
Pathology	Highly specialized	Variable, limited availability	Low specialty
Support services[a]	Not available	Usually available	Available, but pediatric expertise may be limited
On-site imaging facilities	Ultrasound	Ultrasound, CT scans, MRI	Ultrasound, CT scans, MRI
Pediatric anesthesia	Not always available	Always available	Not always available

CT, computed tomography; ICU, intensive care unit; MRI, magnetic resonance imaging. [a]Support services include psychosocial services, parental groups, etc.

twinning initiative or availability of expert consultation for case referral or consult.

Children's hospitals are probably the best choice for developing retinoblastoma programs in most settings 1 and 2, because they are likely to have a pediatric oncology service and palliative care support. Few patients are candidates for eye-conserving therapy, so eye hospitals are usually an inadequate setting as the sole resource for treating children with retinoblastoma in these settings. Building a relationship between a children's hospital and an eye center may enhance treatment options for the few children who are candidates for eye salvage. In most instances of setting 3, children with retinoblastoma may be appropriately treated in any type of center, provided that adequate resources and personnel are available.

The availability of expert pathologists who have the skills to comprehensively assess eye tumors is usually lacking in children's hospitals in settings 1 and 2, and treatment tailored to risk factors associated with pathologic findings may be misleading [17]. A recent report from the Children's Oncology Group showed that even in a high-income country, treating institutions misclassified the risk group assessment in 16% of cases [18]. Training specialized pathologists would result in a more accurate use of adjuvant chemotherapy and it is, therefore, a priority in these settings [19]. Radiotherapy may still play an important role in the treatment regimen of children with retinoblastoma in settings 1 and 2; however, its availability is usually limited to adult cancers, and cobalt is often the only radiation available. In some settings, radiotherapy is not available for children with retinoblastoma.

Although their value has not been unequivocally established, retinoblastoma awareness campaigns directed to the public and doctors may be important in settings 1 and 2, where metastatic disease is present in a high proportion of children at diagnosis [20]. The impact of such campaigns in setting 3 may be lower, because most patients in that setting present with intraocular disease. In all settings, awareness campaigns should target familial cases, because in some middle-income countries, as many as 75% of familial retinoblastoma cases are not screened [21].

STAGING OF DISEASE

A disease-staging system for children with retinoblastoma is essential for the initial evaluation of the extent of extraretinal dissemination and prediction of survival. The International Retinoblastoma Staging System (IRSS) is easily applicable [22]. Ideally, all patients should undergo a complete ophthalmological examination under anesthesia, including tonometry and slit-lamp examination, by an experienced ophthalmologist using indirect ophthalmoscopy. In programs where conservative therapy is undertaken with chemoreduction and localized therapy, a digital camera for documenting the fundoscopic findings may be helpful. Each eye should be assessed according to the International Classification of Intraocular Retinoblastoma [23] or others. At least a head and orbital contrast-enhanced computed tomography (CT) scan should be done, but magnetic resonance imaging (MRI) is preferable, if available, because MRI provides a more accurate imaging of the optic nerve extension.

Although the use of routine examinations of the CSF and bone marrow was questioned in publications from more developed countries [24], in developing countries with higher prevalence of extraocular disease, these procedures should be done more frequently [25], especially to distinguish between stage III (locoregional dissemination and still curable) and stage IV (metastatic dissemination and incurable when high dose therapies are not available) retinoblastoma. A lumbar puncture with examination of the cytocentrifugate and an extensive bone marrow evaluation, preferably including at least two sites, of both the aspirate for cytology and biopsies, should be done in all patients with stage 2 or more progressed disease [25]. This procedure needs to be done under general anesthesia, which is not always available or recommended in children with advanced disease in low-income countries. Alternatively, a single bone marrow aspiration could be done, and if the results are positive, no other bone marrow study is needed. However, when a single aspiration fails to show malignant cells, a more exhaustive bone marrow evaluation should be done. This especially important when it is necessary to discriminate between stages III and IV, because children with stage IV disease benefit from more intensive chemotherapy with autologous stem cell rescue [26]. On the other hand, in setting 2, where some children with stage III retinoblastoma are curable, it may be important to identify those with metastatic disease who would not be cured by lower-intensity therapy. The value of these examinations in cases of stage I disease, even for those with pathologic risk factors, is debatable.

TREATMENT OF OVERT EXTRAOCULAR RETINOBLASTOMA

Overt extraocular retinoblastoma, regardless of the laterality, is classified as IRSS stages III or IV. Children with overt extraocular retinoblastoma usually present with severe pain caused

by an orbital mass [27]. They are frequently emaciated, and their quality of life significantly improves with chemotherapy and supportive measures, but intensive regimens are usually not tolerable.

Retinoblastoma is a highly chemosensitive tumor that responds well to many low-cost chemotherapeutic agents, so they should be offered to all children. Standard-dose chemotherapy with an intention of life prolongation should be given to children with stage IV disease in settings where treatment with high-dose chemotherapy and autologous stem cell rescue are not available. High dose chemotherapy followed by autologous stem cell rescue is the only effective therapy for patients with stage IV extraocular retinoblastoma [28–30]; the cure rate may be as high as 70% if there is no CNS involvement, but it is still lower than 30% in those with CNS involvement [31].

Chemotherapy options include the combination of cyclophosphamide,which may be administered orally, and vincristine or carboplatin and etoposide (Tables III and IV), which seldom cause severe toxicity. Intrathecal chemotherapy may be considered when leptomeningeal dissemination is present but not when contraindicated by a CNS mass. The evidence supporting the use of intrathecal chemotherapy, however, is limited [32,33]. The use of radiotherapy after the orbital or CNS disease has shrunk in response to chemotherapy may also improve the quality of life of these children.

Children with stage III retinoblastoma may be curable with intensive therapy [34], which is available in some centers in setting 2 and in all centers in setting 3, but the results in setting 1 are poorer [35]. Upfront surgery should not be attempted in children with stage III disease. Orbital exenteration is usually not recommended but may be necessary in those with poor response to neoadjuvant chemotherapy. These patients should be treated aggressively with a curative intent using carboplatin-based regimens and orbital radiotherapy (Table IV). However, a subgroup of children with stage III disease and massive enlargement of the optic nerve do poorly with this approach [36].

TREATMENT OF UNILATERAL RETINOBLASTOMA

Upfront enucleation is the treatment of choice for children with intraocular unilateral retinoblastoma. In developed countries, fewer than 1% of these children present with buphthalmia [37], and fewer than 20% present with significant risk factors upon pathology examination [38]. Thus, in more than 95% of cases, enucleation results in complete removal of the tumor, and fewer than 5% have microscopically residual disease after enucleation.

In many countries classified as setting 1, as many as two thirds of children present with enlarged eyeballs, many of whom have microscopic extraocular dissemination [35,39]. Enlarged eyes may be difficult to enucleate and are at high risk of rupture [40], which would seed the tumor in the orbit, thereby theoretically increasing the risk of death and necessitating intensive chemotherapy and orbital radiotherapy. In addition, the tumor may be left behind in the resection margin of the optic nerve. Theoretically, pre-enucleation chemotherapy should reduce tumoral volume in severely buphthalmic eyes, thereby reducing the risk of eye rupture and tumoral residue at the optic nerve margin [40]. This especially important in settings where no radiotherapy is available since children with this condition need it for tumor control [41].

Extraocular extension of disease may be difficult to assess when only low-resolution CT scans are available; gross invasion to the optic nerve or extrascleral invasion may be missed. Thus, clinical–pathological correlations may be important for initial management [42]. In centers where pathology is poor or not available, older age at presentation, longer lag time from the onset of symptoms to diagnosis, presence of hyphema, pseudohypopyon, staphyloma, massive bupthalmia, and history of orbital cellulitis may provide a valuable indication for considering adjuvant chemotherapy in such cases after enucleation [42]. In these children, preoperative chemotherapy to shrink the tumor may facilitate enucleation easier without tumor residue [40,43]. In these instances, these children should be considered at higher risk for extraocular relapse and adjuvant chemotherapy should always be used, regardless of the pathologic findings upon examination of the enucleated eye [44,45]. Enucleation should not be performed later than 2 or 3 chemotherapy cycles, because chemotherapy resistance may ensue, and the child may die of disseminated disease [46]. Even when tumor response to neoadjuvant chemotherapy is spectacular, enucleation is still required.

The choice of chemotherapy regimen depends on the local availability of chemotherapy drugs and the supportive care facilities. Carboplatin-based regimens should be the first choice [47], but if this drug is not available, a regimen including cyclophosphamide and vincristine, with the possible addition of doxorubicin [16], may be an alternative (Table IV).

In cases in which parents consent to upfront enucleation and expert surgery and pathologic assessment are available, enucleation of the affected eye should be performed as soon as extraocular disease has been ruled out. Adjuvant therapy should be instituted after pathologic examination of the enucleated eye per international standards [48]. Adjuvant chemotherapy is necessary for children with postlaminar optic nerve involvement [49,50], with or without tumor in the resection margin, or any degree of scleral involvement [51]. Its use in children with other risk factors and lower risk of extraocular relapse should be balanced with the potential toxicity of chemotherapy and the availability of second-line therapy in a given setting [52].

Children with isolated choroidal or anterior segment invasion have a low risk of relapse (<5%); thus, when treating these patients with adjuvant chemotherapy three issues should be considered: (1) The risk of toxicity-related death during a neutropenic episode or other toxic event may outweigh the benefit of adjuvant chemotherapy in children with low-risk disease, (2) high-quality pathology assessments are essential, and (3) high-dose chemotherapy and stem cell rescue must be available for treatment of relapse. Before withdrawing chemotherapy in children with isolated massive choroidal invasion, an experienced ocular pathologist following international standards should provide a full examination of the enucleated eyeball [48] to ensure that scleral or postlaminar optic nerve invasion, which would require adjuvant therapy, are not present. Because advanced pathologic assessments may not be available in many centers, using adjuvant chemotherapy to treat all children may be a safer approach. More intensive regimens may yield better results in children with high-risk disease [51,53], but they may also be associated

TABLE III. Treatment Recommendations and Evidence Levels Determined by Parental Compliance and Setting

Disease classification	Setting 1	Setting 2	Setting 3
Intraocular unilateral retinoblastoma	Upfront enucleation or alternatively, preoperative chemotherapy followed by enucleation in cases of treatment refusal (Regimen 1 or 2; level 4) Adjuvant chemotherapy to all patients (Regimen 1 or 2; level 4)	Upfront enucleation followed by adjuvant chemotherapy according to risk (Regimen 1; level 3iiA) [70]	Upfront enucleation followed by adjuvant chemotherapy according to risk (Regimens 3–5; level 3iiA) [53,73]
Orbital retinoblastoma	Preoperative chemotherapy followed by secondary enucleation. Adjuvant chemotherapy and radiotherapy (Regimen 1 or 2; level 3iiA) [27]	Preoperative chemotherapy followed by secondary enucleation. Adjuvant chemotherapy and radiotherapy (Regimens 1 and 6; level 3iiA) [70]	Preoperative chemotherapy followed by secondary enucleation. Adjuvant chemotherapy and radiotherapy (Regimens 3–5; level 3iiA) [53,73]
Metastatic retinoblastoma (unilateral or bilateral)	Palliative care and low dose chemotherapy (Regimens 2 and 6; level 4)	Palliative care and low dose chemotherapy (Regimens 2 and 6; level 4)	Neoadjuvant chemotherapy, followed by local control and consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue (in responding patients; level 3iiA) [26]
Conservative therapy for unilateral disease	Not recommended (level 4)	Only for selected cases of groups A–C eyes, where chemoreduction and local therapy can be safely provided (Regimen 1; level 4)	Only for selected cases of group A–C eyes where chemoreduction and local therapy (Regimen 1; level 3iiDi) [61] or intra-arterial chemotherapy can be provided (level 3iiDiii) [65,66]
Conservative therapy for bilateral retinoblastoma	Enucleation of group D and E eyes (level 4) Conservative therapy is usually not possible and need to be considered only in cases of groups A–C eyes where follow-up could be ascertained (Regimen 1) EBRT (where available) where treatment compliance is poor (level 4)	Enucleation of group D–E eyes (level 3iiA) [3] For group A–C eyes, chemoreduction and local therapy (Regimen 1) where available and adequate follow-up should be ascertained (level 3iiDi) [70] Chemoreduction followed by EBRT (Regimen 1) where localized therapy is not available (level 4) EBRT when treatment compliance is a problem (level 4)	Enucleation of group E eyes (level 3iiA) [3] For group A–C eyes, chemoreduction, and local therapy (Regimen 1; level 3iiDi) [60,61] For group D eyes, enucleation if contralateral eye is group A–C (level 3iiDi) [60,61] Chemoreduction and EBRT when needed if bilateral group D eyes (level 3iiDi) or if contralateral eye is group E [60,61]

TABLE IV. Published Chemotherapy Regimens and Their Indications

Chemotherapy regimen[a]	Possible use (level of evidence of the recommendation)	Advantages	Disadvantages	Refs.
1) Carboplatin (500–560 mg/m^2 on Day 1) + Etoposide (100–150 mg/m^2 on Days 1–2) + Vincristine (1.5 mg/m^2 on Day 1 ([a])	Chemoreduction (setting 2 and 3) (level 3iiDi) Adjuvant therapy (setting 1 and 2) (level 3iiA) Neoadjuvant therapy (setting 1) (level 3iiA)	Low mortality related to toxicity High availability Low cost Ambulatory	May be insufficient for adjuvant therapy in children with high-risk disease	[54,55,61]
2) Cyclophosphamide (40 mg/kg on Day 1) + Vincristine (1.5 mg/m^2 on Day 1) ± Doxorubicin (30 mg/m^2 on Day 1)	Palliative therapy (level 4)[b] Adjuvant therapy (if carboplatin is not available) (level 3iiA)	Low toxicity Low cost Good antitumor activity Ambulatory	May be insufficient as adjuvant therapy Long-term gonadal and cardiac toxicity	[15,16]
3) Carboplatin (500 mg/m^2 on Days 1–2) + Etoposide (100 mg/m^2 on Days 1–3)	Chemoreduction for advanced cases (setting 3) (level 4) Adjuvant therapy (setting 3) (level 3iiA) Neoadjuvant therapy (setting 3) (level 3iiA) Treatment of metastatic disease (setting 3) (level 3iiA)	Good CNS penetration Probably more effective as adjuvant therapy (associated with Regimen 4) in patients with high-risk disease (compared to Regimen 1)	Highly myelotoxic Superiority over lower doses is not known High cumulative doses of etoposide	[72]
4) Cyclophosphamide (65 mg/kg on Day 1) + Vincristine (1.5 mg/m^2 on Day 1) + Idarubicin[c] (10 mg/m^2 on Day 1)	Adjuvant therapy (setting 3) (level 3iiA) Neoadjuvant therapy (setting 3) (level 3iiA) Treatment of metastatic disease (setting 3) (level 3iiA)	Good CNS penetration Not cross-resistant to carboplatin-based drugs	The use of anthracyclines has not been proven to improve results Gonadal toxicity	[72]
5) Ifosfamide (1.8 g/m^2 on Days 1–5) + Etoposide (100 mg/m^2 on Days 1–5) ± Carboplatin (400 mg/m^2 on Days 1 and 2)	Adjuvant therapy (setting 3) (level 3iiA) Neoadjuvant therapy (setting 3) (level 3iiiDiv) Treatment of metastatic disease (setting 3) (level 4)	Good CNS penetration Not cross-resistant combination	Ifosfamide-induced nephrotoxicity in small children Inpatient administration Highly myelotoxic Gonadotoxic	[37,56]
Intrathecal chemotherapy (cytarabine or topotecan)	Palliative treatment of leptomeningeal dissemination. (level 4)[b] Possible role as further prevention of CNS relapses when low-dose adjuvant therapy is given (level 4)	Easy to administer Limited toxicity Low cost	Efficacy not proven	[15,32,33]

[a]Dose modification may be necessary for children weighing less than 10 to 12 kg. Proposed dosages: Vincristine (0.05 mg/kg, IV), doxorubicin (1–2 mg/kg per dose), carboplatin (16–18 mg/kg per dose), etoposide (3.3–5 mg/kg per dose); [b]Cyclophosphamide (20 mg/kg orally at night, 2 h after meals) may be given as palliative therapy (level 4); [c]May be replaced by doxorubicin (30 mg/m^2 on Day 1).

with increased risk of toxicity-related death in settings with limited resources. Thus, the benefit of preventing extraocular relapse may be outweighed by the risk of toxic death. Therefore, more intensive regimens should be used only in setting 3 and preferably under prospective protocols.

TREATMENT OF BILATERAL RETINOBLASTOMA

Conservative therapy is usually not a priority in setting 1, where most children die of extraocular retinoblastoma. Enucleation would cure a high proportion of children with bilateral retinoblastoma, so it is important that patients with intraocular disease not be exposed to treatments with conservative intent in a setting that has no facilities or experience in localized therapy. Chemoreduction followed by focal therapy to avoid EBRT, the standard conservative treatment in developed countries [54,55], may not be feasible in developing countries, because most children there present with advanced disease requiring EBRT or enucleation. This treatment is particularly dangerous in settings with a high rate of abandonment of follow-up, because partially treated tumors may reactivate and disseminate [56,57].

Telemedicine facilities are helpful during follow-up [58]. Late relapses tend to occur [59], even in those whose disease was treated appropriately. Thus, patients lost to follow-up may be at a higher risk of mortality [56]. Chemoreduction may be advantageous in cases in which pathologic assessment of the contralateral enucleated eye shows risk factors indicating the need for adjuvant chemotherapy. As a general rule, conservative therapy of Group D eyes should not be considered routinely in centers with limited resources in setting 2, because their preservation rate is low, especially if EBRT is not available. In most centers in setting 3 and some in setting 2, state-of-the-art conservative treatments are possible [60,61]. Centers of excellence have been created in many countries that are capable of providing state-of-the-art conservative treatment by adequately trained, experienced teams.

The only benefit of chemoreduction is avoiding or delaying EBRT, which is associated with 6–17% increased risk of mortality caused by radiation-induced second tumors during adulthood in developed countries [62,63]. To justify the use of chemoreduction over EBRT, toxic mortality associated with a regimen such as standard CEV (Regimen 1, Table IV) should be less than 1–2%. Avoidance of EBRT not only decreases the risk of secondary malignancies but also results in better cosmesis and lower prevalence of ocular side effects. However, in terms of ocular salvage, no benefit has been proven. Patients treated with EBRT need less-intensive follow-up and are likely to be cured with one 6-week course of radiotherapy, whereas children treated with chemoreduction and local therapy usually need a more intensive, longer follow-up to consolidate tumor response and treat later relapses. However, surgery for repairing radiation-induced cataracts that occur in almost all patients within a few years of irradiation should be available [64]. Therefore, the availability of a high-quality EBRT facility is a priority in this scenario, especially in setting 2. Training of EBRT personnel is also a challenge in developing countries. In setting 3, most resources for localized therapy are available, but more cases with advanced disease are likely to be seen, so second-line therapy should be available.

Intra-arterial chemotherapy is widely used in developed countries [65] and has become gradually available in some developing countries (setting 3) [66,67]. This modality may be important for treating eyes with advanced disease or as secondary treatment, but it should be used with caution as initial treatment because of the higher prevalence of eyes with pathologic risk factors in this setting. Intra-arterial chemotherapy is usually not recommended for initial treatment of most cases of unilateral disease, which are best managed by enucleation in developing countries. Adjuvant therapy for enucleated eyes in cases of bilateral retinoblastoma should follow the same guidelines as those for cases of unilateral disease.

MANAGEMENT OF CASES IN WHICH PARENTS REFUSE RECOMMENDED THERAPY

Treatment compliance is a substantial problem that occurs in many developing countries [68]. This is critically important in cases of intraocular retinoblastoma requiring enucleation, because some patients could be cured by this simple surgical procedure. If left untreated, retinoblastoma is uniformly fatal. As many as one third of the patients in a series from Indonesia abandoned therapy temporarily [4]; but this may occur in as many as 75% of cases in other settings [69]. Some patients returned for medical care but only after the globe became grossly proptotic and metastatic disease occurred, at which time it was too late; fewer than 20% were cured [4]. As many as 18% of patients never came back; they probably died of disease [4].

Centers where compliance is a substantial problem should establish a comprehensive program to approach these families. Poor compliance to therapy is associated with poor socioeconomic conditions, especially in settings where anticancer treatment is not free of charge [68]. In other situations, cultural and/or religious reasons may limit the acceptance of enucleation. In large countries with geographic barriers, patients are usually admitted to hospitals in large cities, and their mothers are usually the sole caregiver. In some settings, mothers need the approval of the extended family for procedures such as enucleation. Actions to improve compliance should be actively pursued. Successful experiences have been reported in Central America [70], where families of children with high-risk disease are approached by a multidisciplinary team and given special support [70]. In that setting, the rate of treatment refusal decreased from 21% of patients in 2000–2003 to 11% in 2004–2008 after an intervention program. Aspects of the care that likely led to decreased refusal rate included twinning with established centers of excellence via internet-based consultations, donations of equipment, and sponsoring the Central American ophthalmologists to attend international conferences as well as providing training locally [71]. This program also provided prosthesis and other centers use a provisional prosthesis in the operating room after enucleation, so that the families tolerate the procedure better. Parental groups play a key role providing emotional support, contact with survivors who are living normal lives, and financial support are important to preventing treatment refusal.

Therefore, in addition to these general guidelines that are applicable to all settings, specific recommendations for the management of patients whose families refuse enucleation in each setting include:

Settings 1 and 2: Especially in centers where expert pathology examination is not available, these patients may treated with pre-enucleation chemotherapy followed by adjuvant therapy (Table III). Despite the fact that pre-enucleation chemotherapy

may obscure the pathology of the enucleated eye, the reported results in setting 2 favor pre-enucleation chemotherapy in patients with poor compliance [4,44]. Many families that do not consent to initial enucleation do consent to chemotherapy [72]. This provides time to approach the families, in a multidisciplinary fashion, to reconsider their decision. In these situations, the clinician must balance the risks and benefits of this approach. The risks include chemotherapy-related toxicity, including death, in children who do not clearly benefit from it. Chemotherapy also may alter the pathology of the enucleated eye in such a way that compromises the accuracy of the assessment of risk of extraocular relapse [44]. These risks must be weighed against the fact that if no chemotherapy is given, the child will die in more than 80% of the cases [4]. Chemotherapy in this situation may improve the results of children from families who temporarily refuse enucleation. Therefore, clinicians should either not administer any therapy while approaching the families about consenting to enucleation or administer chemotherapy in the meantime. No prospective studies have compared these approaches and there may be regional variations in the efficacy of this approach in each setting. If chemotherapy is chosen, it should be done as a last resort, to prevent imminent drop out. Tumor response is almost always seen with chemotherapy; however, this does not imply that the diseased eye can become salvageable. No focal therapy should be administered to the eye, and enucleation should be done as soon as the family consents to it.

A recent retrospective series from China [44] and preliminary data from a prospective multicenter study from Central America [41] have shown a survival rate greater than 80% in children with retinoblastoma whose families were at high risk of treatment abandonment, when the child was given pre-enucleation chemotherapy. The survival results from the Chinese series were inferior to those seen in children whose families consented to enucleation upfront [44]. The authors were concerned that pre-enucleation chemotherapy increases mortality, because the pathologic features of the enucleated eye may be interpreted inaccurately after chemotherapy. Thus, children may not receive adequate post-surgical therapy [44]. Although this may explain the poorer survival results, compared to those of children who received adequate therapy, all of the patients who suffered extraocular relapse had undergone a very late enucleation, often after more than six chemotherapy cycles. This delay led to extraocular dissemination before enucleation, which was evident in four of five relapsed cases. Delayed enucleation was caused by a lack of treatment compliance [45].

Setting 3: Refusal of enucleation is less common in this setting [1] and pre-enucleation chemotherapy has been used less frequently [72]. In this setting as well as in selected cases of setting 2, the necessary legal framework in support of the Children's Bill of Rights are usually available, so parental refusal of treatment for their child should be addressed via the legal support systems when other supporting alternatives have failed.

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REFERENCES

1. Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. Br J Ophthalmol 2010;94:1432–1436.
2. Kivela T. The epidemiological challenge of the most frequent eye cancer: Retinoblastoma, an issue of birth and death. Br J Ophthalmol 2009;93:1129–1131.
3. Sultan I, Wilson MW, Nawaiseh I, et al. Enucleation for retinoblastoma: The experience of a single center in Jordan. Int Ophthalmol 2010;30:407–414.
4. Sitorus RS, Moll AC, Suhardjono S, et al. The effect of therapy refusal against medical advice in retinoblastoma patients in a setting where treatment delays are common. Ophthalmic Genet 2009; 30:31–36.
5. Gupta R, Vemuganti GK, Reddy VA, et al. Histopathologic risk factors in retinoblastoma in India. Arch Pathol Lab Med 2009;133:1210–1214.
6. Leal-Leal CA, Rivera-Luna R, Flores-Rojo M, et al. Survival in extra-orbital metastatic retinoblastoma: Treatment results. Clin Transl Oncol 2006;8:39–44.
7. Shields CL, Shields JA. Retinoblastoma management: Advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. Curr Opin Ophthalmol 2010;21:203–212.
8. Wilson MW, Haik BG, Rodriguez-Galindo C. Socioeconomic impact of modern multidisciplinary management of retinoblastoma. Pediatrics 2006;118:e331–e336.
9. Shields CL, Ramasubramanian A, Thangappan A, et al. Chemoreduction for group E retinoblastoma: Comparison of chemoreduction alone versus chemoreduction plus low-dose external radiotherapy in 76 eyes. Ophthalmology 2009;116:544–551, e541.
10. Friedman DL, Himelstein B, Shields CL, et al. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol 2000;18:12–17.
11. National Cancer Institute PDQ® Levels of Evidence for Adult and Pediatric Cancer Treatment Studies. Last update 08/26/2010, accessed 11/02/2012. In Edition Bethesda: National Cancer Institute 2012.
12. Hunger SP, Sung L, Howard SC. Treatment strategies and regimens of graduated intensity for childhood acute lymphoblastic leukemia in low-income countries: A proposal. Pediatr Blood Cancer 2009;52:559–565.
13. Gallie B. Canadian guidelines for retinoblastoma care. Can J Ophthalmol 2009;44:639–642.
14. Rodriguez-Galindo C, Wilson MW, Chantada G, et al. Retinoblastoma: One world, one vision. Pediatrics 2008;122:e763–e770.
15. Schvartzman E, Chantada G, Fandino A, et al. Results of a stage-based protocol for the treatment of retinoblastoma. J Clin Oncol 1996;14:1532–1536.
16. Mustafa MM, Jamshed A, Khafaga Y, et al. Adjuvant chemotherapy with vincristine, doxorubicin, and cyclophosphamide in the treatment of postenucleation high risk retinoblastoma. J Pediatr Hematol Oncol 1999;21:364–369.
17. Bowman RJ, Mafwiri M, Luthert P, et al. Outcome of retinoblastoma in east Africa. Pediatr Blood Cancer 2008;50:160–162.
18. Chintagumpala M LB Eagle R, Albert D, et al. A large prospective trial of children with unilateral retinoblastoma with and without histopathologic high-risk features and the role of adjuvant chemotherapy: A Children's Oncology Group (COG) study. In ASCO. Annual Meeting, Edition 2012.
19. Sengupta S, Krishnakumar S, Sharma T, et al. Histopathology of retinoblastoma: Does standardization make a difference in reporting? Pediatr Blood Cancer 2013;60:336–337.
20. Leander C, Fu LC, Pena A, et al. Impact of an education program on late diagnosis of retinoblastoma in Honduras. Pediatr Blood Cancer 2007;49:817–819.
21. Chantada GL, Dunkel IJ, Qaddoumi I, et al. Familial retinoblastoma in developing countries. Pediatr Blood Cancer 2009;53:338–342.
22. Chantada G, Doz F, Antoneli CB, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 2006;47:801–805.
23. Linn Murphree A. Intraocular retinoblastoma: The case for a new group classification. Ophthalmol Clin North Am 2005;18:41–53, viii.
24. Zacharoulis S, Abramson DH, Dunkel IJ. More aggressive bone marrow screening in retinoblastoma patients is not indicated: The memorial Sloan-Kettering cancer center experience. Pediatr Blood Cancer 2006;46:56–61.
25. Bakhshi S, Meel R, Kashyap S, et al. Bone marrow aspirations and lumbar punctures in retinoblastoma at diagnosis: Correlation with IRSS staging. J Pediatr Hematol Oncol 2011;33:e182–e185.
26. Palma J, Sasso DF, Dufort G, et al. Successful treatment of metastatic retinoblastoma with high-dose chemotherapy and autologous stem cell rescue in South America. Bone Marrow Transplant 2012; 47:522–527.
27. Ali MJ, Reddy VA, Honavar SG, et al. Orbital retinoblastoma: Where do we go from here? J Cancer Res Ther 2011;7:11–14.
28. Namouni F, Doz F, Tanguy ML, et al. High-dose chemotherapy with carboplatin, etoposide and cyclophosphamide followed by a haematopoietic stem cell rescue in patients with high-risk retinoblastoma: A SFOP and SFGM study. Eur J Cancer 1997;33:2368–2375.
29. Dunkel IJ, Aledo A, Kernan NA, et al. Successful treatment of metastatic retinoblastoma. Cancer 2000;89:2117–2121.
30. Cozza R, De Ioris MA, Ilari I, et al. Metastatic retinoblastoma: Single institution experience over two decades. Br J Ophthalmol 2009;93:1163–1166.
31. Dunkel IJ, Chan HS, Jubran R, et al. High-dose chemotherapy with autologous hematopoietic stem cell rescue for stage 4B retinoblastoma. Pediatr Blood Cancer 2010;55:149–152.
32. Chan HS, Canton MD, Gallie BL. Chemosensitivity and multidrug resistance to antineoplastic drugs in retinoblastoma cell lines. Anticancer Res 1989;9:469–474.
33. Blaney SM, Heideman R, Berg S, et al. Phase I clinical trial of intrathecal topotecan in patients with neoplastic meningitis. J Clin Oncol 2003;21:143–147.
34. Doz F, Khelfaoui F, Mosseri V, et al. The role of chemotherapy in orbital involvement of retinoblastoma. The experience of a single institution with 33 patients. Cancer 1994;74:722–732.
35. Carrim ZI, Kajaige J, Bowman RJ, et al. First-year experience of chemotherapy for advanced retinoblastoma in Tanzania: Disease profile, outcomes, and challenges in 2008. J Pediatr Ophthalmol Strabismus 2012;49:176–183.

36. Radhakrishnan V, Kashyap S, Pushker N, et al. Outcome, pathologic findings, and compliance in orbital retinoblastoma (International Retinoblastoma Staging System Stage III) treated with neoadjuvant chemotherapy: A prospective study. Ophthalmology 2012;119:1470–1477.
37. Abramson DH, Frank CM, Susman M, et al. Presenting signs of retinoblastoma. J Pediatr 1998;132:505–508.
38. Eagle RC, Jr. High-risk features and tumor differentiation in retinoblastoma: A retrospective histopathologic study. Arch Pathol Lab Med 2009;133:1203–1209.
39. Bhurgri Y, Muzaffar S, Ahmed R, et al. Retinoblastoma in Karachi, Pakistan. Asian Pac J Cancer Prev 2004;5:159–163.
40. Bellaton E, Bertozzi AI, Behar C, et al. Neoadjuvant chemotherapy for extensive unilateral retinoblastoma. Br J Ophthalmol 2003;87:327–329.
41. Luna-Fineman S, Alejos A, Amador G, et al. Pre-enucleation chemotherapy in advanced intraocular retinoblastoma. Central American experience: AHOPCA II. Pediatr Blood Cancer 2012; 59:984.
42. Kashyap S, Meel R, Pushker N, et al. Clinical predictors of high risk histopathology in retinoblastoma. Pediatr Blood Cancer 2012;58:356–361.
43. Armenian SH, Panigrahy A, Murphree AL, et al. Management of retinoblastoma with proximal optic nerve enhancement on MRI at diagnosis. Pediatr Blood Cancer 2008;51:479–484.
44. Zhao J, Dimaras H, Massey C, et al. Pre-enucleation chemotherapy for eyes severely affected by retinoblastoma masks risk of tumor extension and increases death from metastasis. J Clin Oncol 2011;29:845–851.
45. Chantada G, Leal-Leal C, Brisse H, et al. Is it pre-enucleation chemotherapy or delayed enucleation of severely involved eyes with intraocular retinoblastoma that risks extraocular dissemination and death? J Clin Oncol 2011;29:3333–3334; author reply 3335–3336.
46. Bai S, Ren R, Li B, et al. Delay in the diagnosis of retinoblastoma in China. Acta Ophthalmol 2011;89:e72–e74.
47. Doz F, Neuenschwander S, Plantaz D, et al. Etoposide and carboplatin in extraocular retinoblastoma: A study by the Societe Francaise d'Oncologie Pediatrique. J Clin Oncol 1995;13:902–909.
48. Sastre X, Chantada GL, Doz F, et al. Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. Arch Pathol Lab Med 2009;133:1199–1202.
49. Chantada GL, Dunkel IJ, de Davila MT, et al. Retinoblastoma patients with high risk ocular pathological features: Who needs adjuvant therapy? Br J Ophthalmol 2004;88:1069–1073.
50. Chantada GL, Casco F, Fandino AC, et al. Outcome of patients with retinoblastoma and postlaminar optic nerve invasion. Ophthalmology 2007;114:2083–2089.
51. Cuenca A, Giron F, Castro D, et al. Microscopic scleral invasion in retinoblastoma: Clinicopathological features and outcome. Arch Ophthalmol 2009;127:1006–1010.
52. Bosaleh A, Sampor C, Solernou V, et al. Outcome of children with retinoblastoma and isolated choroidal invasion. Arch Ophthalmol 2012;130:724–729.
53. Antoneli CB, Ribeiro KB, Rodriguez-Galindo C, et al. The addition of ifosfamide/etoposide to cisplatin/teniposide improves the survival of children with retinoblastoma and orbital involvement. J Pediatr Hematol Oncol 2007;29:700–704.
54. Kingston JE, Hungerford JL, Madreperla SA, et al. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Arch Ophthalmol 1996;114:1339–1343.
55. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: Factors predictive of need for treatment with external beam radiotherapy or enucleation. Am J Ophthalmol 2002;133:657–664.
56. Menon BS, Juraida E, Alagaratnam J, et al. Chemoreduction for intraocular retinoblastoma in Malaysia. J Pediatr Hematol Oncol 2007;29:2–4.
57. Bakhshi S, Gupta S, Gogia V, et al. Compliance in retinoblastoma. Indian J Pediatr 2010;77:535–540.
58. Qaddoumi I, Nawaiseh I, Mehyar M, et al. Team management, twinning, and telemedicine in retinoblastoma: A 3-tier approach implemented in the first eye salvage program in Jordan. Pediatr Blood Cancer 2008;51:241–244.
59. Shields CL, Shelil A, Cater J, et al. Development of new retinoblastomas after 6 cycles of chemoreduction for retinoblastoma in 162 eyes of 106 consecutive patients. Arch Ophthalmol 2003;121:1571–1576.
60. Chantada GL, Fandino AC, Raslawski EC, et al. Experience with chemoreduction and focal therapy for intraocular retinoblastoma in a developing country. Pediatr Blood Cancer 2005;44:455–460.
61. Antoneli CB, Ribeiro KC, Steinhorst F, et al. Treatment of retinoblastoma patients with chemoreduction plus local therapy: Experience of the AC Camargo Hospital, Brazil. J Pediatr Hematol Oncol 2006;28:342–345.
62. Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. Br J Cancer 1986;53:661–671.
63. Marees T, van Leeuwen FE, de Boer MR, et al. Cancer mortality in long-term survivors of retinoblastoma. Eur J Cancer 2009;45:3245–3253.
64. Chodick G, Kleinerman RA, Stovall M, et al. Risk of cataract extraction among adult retinoblastoma survivors. Arch Ophthalmol 2009;127:1500–1504.
65. Gobin YP, Dunkel IJ, Marr BP, et al. Intra-arterial chemotherapy for the management of retinoblastoma: Four-year experience. Arch Ophthalmol 2011;129:732–737.
66. Schaiquevich P, Ceciliano A, Millan N, et al. Intra-arterial chemotherapy is more effective than sequential periocular and intravenous chemotherapy as salvage treatment for relapsed retinoblastoma. Pediatr Blood Cancer 2012; DOI: 10.1002/pbc.24356. [Epub ahead of print].
67. Trinavarat A, Chiewvit P, Buaboonnam J, et al. Selective ophthalmic arterial infusion of chemotherapeutic drugs for recurrent retinoblastoma. J Pediatr Hematol Oncol 2012;34:e218–e221.
68. Mostert S, Arora RS, Arreola M, et al. Abandonment of treatment for childhood cancer: Position statement of a SIOP PODC Working Group. Lancet Oncol 2011;12:719–720.
69. Kazadi Lukusa A, Aloni MN, Kadima-Tshimanga B, et al. Retinoblastoma in the democratic republic of congo: 20-Year review from a tertiary hospital in kinshasa. J Cancer Epidemiol 2012;2012:920468.
70. Luna-Fineman S, Barnoya M, Bonilla M, et al. Retinoblastoma in Central America: Report from the Central American Association of Pediatric Hematology Oncology (AHOPCA). Pediatr Blood Cancer 2012;58:545–550.
71. Wilimas JA, Wilson MW, Haik BG, et al. Development of retinoblastoma programs in Central America. Pediatr Blood Cancer 2009;53:42–46.
72. Chantada GL, Fandino AC, Guitter MR, et al. Results of a prospective study for the treatment of unilateral retinoblastoma. Pediatr Blood Cancer 2010;55:60–66.