HOW WE APPROACH CONSERVATIVE TREATMENT OF RETINOBLASTOMA IN SOUTH AMERICA IN THE ERA OF LOCAL OCULAR TREATMENTS. A CONSENSUS OF THE GRUPO AMERICA LATINA DE ONCOLOGIA PEDIATRICA (GALOP)

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Abstract

Local therapies replaced systemic chemotherapy for ocular preservation in retinoblastoma. In middle income countries, these techniques pose specific challenges mostly related to more advanced disease at diagnosis. The Grupo de America Latina de Oncologia Pediatrica (GALOP developed a consensus document for the management of conservative therapy for retinoblastoma. Intra-arterial chemotherapy (OAC) is the preferred therapy, except those with less advanced disease or age younger than 6 months. OAC allowed for the elimination of the use of external beam radiotherapy in our setting. Intravitreal chemotherapy is the preferred treatment for vitreous seeding. Enucleation is the treatment of choice for advanced eyes.

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EBRT	External beam radiotherapy
OAC	Ophthalmic artery chemosurgery
UBM	Ultra bio-microscopy
HRPF	High risk pathology features
Ct DNA	Circulating tumoral DNA

ABSTRACT

Local therapies replaced systemic chemotherapy for ocular preservation in retinoblastoma. In middle income countries, these techniques pose specific challenges mostly related to more advanced disease at diagnosis.

The Grupo de America Latina de Oncologia Pediatrica (GALOP developed a consensus document for the management of conservative therapy for retinoblastoma. Intra-arterial chemotherapy (OAC) is the preferred therapy, except those with less advanced disease or age younger than 6 months. OAC allowed for the elimination of the use of external beam radiotherapy in our setting. Intravitreal chemotherapy is the preferred treatment for vitreous seeding. Enucleation is the treatment of choice for advanced eyes.

BACKGROUND

Since the mid-1990s, conservative treatment of retinoblastoma includes tumor chemoreduction with systemic chemotherapy using Carboplatin, Etoposide and Vincristine followed by focal therapies[1,2]. In our setting, this resulted in an increase rate of ocular preservation while reducing the use of external radiotherapy (EBRT), albeit at the cost of a higher use of resources[3,4] since this treatment is associated with hospitalizations due to chemotherapy complications such as transfusions, neutropenic fever and long-term effects such as ototoxicity as well as chemotherapy-induced acute leukemia[5-7]. In Latin America, up to one third of the patients present with advanced bilateral retinoblastoma, so avoidance of EBRT could be achieved in less than a third of the patients[4]. The results of this treatment in eyes with vitreous or subretinal seeding were modest, therefore, several major institutions in high income countries implemented ocular chemotherapy techniques such as intra-arterial (OAC) and intra-vitreal chemotherapy in order to allow greater delivery of chemotherapy to the eye with fewer systemic effects[8]. As opposed to other pediatric malignancies, these outstanding results were not achieved by international cooperative groups performing prospective studies. Therefore, most referral centers for retinoblastoma in South America also moved from systemic to ocular delivery of chemotherapy for the conservative treatment resulting in unprecedented ocular salvage rates and near total elimination of EBRT[9-11]. This document is the result of a consensus of the current management in institutions participating in the GALOP group, which included collaborating institutions in Spain and Portugal.

INTRA-ARTERIAL CHEMOTHERAPY

In 2008, Abramson and Gobin et al optimized the technique for OAC by directly catheterizing the ophthalmic artery, achieving a so-called "superselective" administration, since the ophthalmic artery was directly accessed allowing for the use of low absolute doses of chemotherapy[12]. The best results were seen in patients with extensive retinal detachment and cases with massive intra-retinal tumors and subretinal seeding[13,14]. No major complications due to the procedure were observed, and only mild adverse events were seen[13]. In Latin America, OAC was first introduced by the Argentinian group after training in New York in 2009 as a result of a long-term collaboration[10,15]. However, as opposed to the North American experience, in Argentina (and later in other Latin American countries), OAC was mostly used for the treatment of relapsed or advanced bilateral disease and less frequently for patients with unilateral disease[9,10]. Later, this treatment was gradually introduced in other countries included in this consensus document[9,11,16].

However, there are still unanswered questions about the use of OAC for retinoblastoma. Current treatments are basically empirical in terms of dose and frequency of treatment. The most widely used drug has been Melphalan, but its use is based on incompletely reported *in vitro*chemosensitivity studies carried out several years ago in Japan[17]. The New York and Argentinian groups, among others, have also used Topotecan and Carboplatin with good results in terms of efficacy and toxicity[10,13]. The pharmacokinetic profile of this combination, described by members of this group, was useful to determine the systemic exposure to drugs and with it, its relationship with toxicity and efficacy, allowing a rational design of the therapeutic scheme of administration of OAC[18,19]. Although many groups use Melphalan as a single agent in this indication, drug combinations tend to be more active in avoiding resistance mechanisms and also useful to reduce toxicity of chemotherapeutic drugs by distributing the different toxicities of various drugs in order to reduce their accumulated doses.

Although the technique is called superselective, predictably, plasma chemotherapy levels are found in patients treated with this modality, being higher in patients receiving treatment in both eyes correlating with myelotoxicity if the dose is greater than 0.48 mg/kg[18]. Topotecan is an attractive agent for OAC because of

its greater vitreous penetration compared to Melphalan[20]. However, no convincing response was seen when used as single agent for OAC[21]. Additionally, in vitro cytotoxicity studies of Topotecan and Melphalan showed that both drugs are synergistic in their activity in human retinoblastoma cell lines[19]. The New York group pioneered the use of carboplatin by this route[22]. Carboplatin has been extensively studied in retinoblastoma, whose activity has been proven from the clinic to animal models[23,24]. No significant toxicity associated to Carboplatin given intra-arterially were reported and in the series from Argentina no differences were observed in terms of ocular preservation in eyes treated with Carboplatin (+/- Topotecan) compared to Melphalan[10,22]. For all these reasons, this consensus proposes a first-line chemotherapy scheme including combinations of the 3 active drugs, Melphalan, Topotecan, and Carboplatin, especially when used as a tandem treatment or for advanced cases.

THE OAC PROCEDURE

It is essential that OAC should be performed by an experienced interventional radiologist or neuro-surgeon, preferably in a center with high patient numbers. The procedure is performed under general anesthesia in the angiography room, with the patient in the supine position. Chemotherapy must be prepared at the oncology pharmacy at the time of administration or, in special circumstances, directly in the angiography suite. Ideally, chemotherapy is requested to the pharmacy as the patient enters the angiography suite so that it is ready for administration at the time of the procedure. After complete disinfection of the groin region, the right or left common femoral artery is punctured. Ultrasound guidance for access may be used in difficult cases, small infants, or according to institutional policies. Following local anesthesia, a 3-French pediatric arterial sheath is placed into the arterial lumen using the Seldinger technique. It is then guided into the internal carotid artery over a 0.008 inch microguide or Sychro 0.010 microguide under fluoroscopic guidance in conjunction with a flow microcatheter (Magic) or microguide-guided microcatheters such as the Marathon microcatheter. In patients older than 4 years, a 4 French Pediatric introducer and a 4 French guide catheter are used. The microcatheters in this group are passed through the 4 French guiding catheter.

Systemic heparinization should be performed intravenously, with an initial heparin bolus of 20 IU/kg. In addition, an intra-arterial catheter drip perfusion (heparinated NaCl solution; 60-70 IU heparin/kg patient weight) is established for the duration of the procedure as a preventive measure against secondary thromboembolism that may be caused by continued presence of the intracarotid catheter.

A flow-guided coaxial microcatheter, 1.2 or 1.5 French (diameter 0.4 and 0.5 mm respectively), is mounted on a 0.007" or 0.014" guide needle, which is directed to the ostium of the ophthalmic artery but not into the artery itself After fluoroscopic confirmation of the correct position of the microcatheter tip as evidenced by a correct choroidal blush, chemotherapy is infused. If an optimal choroidal blush is not obtained or the ophthalmic artery cannot be accessed, it is mandatory to explore an alternative route without further delay, such as use of a micro balloon catheter in the internal carotid artery or catheterization of the external carotid artery (infusing the middle meningeal artery)[25].

The total volume of the drugs to be infused must be 30 ml of 0.9% NaCl, dividing the volumes into 15 ml for the administration of each of the drugs (or 10 ml when the three drugs are used in the same eye). The total duration of the infusion is between 20 and 30 minutes, always using a pulsatile technique to allow the drug to get to the inside wall of the artery since laminar flow would not allow to reach the arterial branches if the drugs are simply infused continuously. The microcatheter must be flushed between the 2 chemotherapy injections. Prior to chemotherapy infusion, anti-emetic treatment with ondansetron should be administered intravenously and some groups add vasoconstrictive drops and sprays to the forehead and into the nose respectively in order to shut off blood supply to the nose and supratrochlear artery.

When the infusion is complete, all catheters and the arterial introducer are removed. Hemostasis is achieved by initial manual compression of the femoral artery for 10 minutes, followed by a pressure bandage held in place for 4 hours. Once extubated, the patient is awakened in the angiography recovery room and then transferred to a day hospital or a post-surgical recovery room according to institutional practice, and subsequently discharged from the hospital after 4-8 hours if no complications occur.

The use of systemic corticosteroids (dexamethasone 0.15 mg/kg) in order to prevent orbital edema is routinely considered in cases when the three drugs are administered in the same eye or when erythema is confirmed at the end of the procedure or orbital edema, especially when an external carotid artery approach has been used. Depending on institutional practice, some groups routinely use corticosteroids eye drops. The use of modern equipment and limited exposure times are essential, in order to deliver a minimum dose of radiation[26].

DRUGS AND DOSAGES FOR OAC

The combination of Melphalan and Topotecan was the preferred initial regimen in this consortium for monocular treatments. Carboplatin may be used in case of lack of availability of Melphalan. If both eyes should be treated, our group recommends tandem OAC (i.e. sequential chemotherapy administration to both eyes in the same procedure)[27]. For bilateral Group D eyes, we agreed to use upfront tandem OAC[27]. In these cases, the chemotherapy combination is decided individually for each patient using the doses indicated in Table 1, but deciding upon the tumor response and tolerance. The most common practice is to give Melphalan-Topotecan to one eye and Carboplatin-Topotecan to the contralateral eye (Table 2). It is possible to alternate this combination in each eye when response is asymmetrical or toxicity occurs. We discourage the routine use of bilateral injections of Melphalan either at full doses or in reduced doses, preferring the use of the 3-drug combination. Factors such as vascular anatomy play an important role in the efficacy of this treatment[25]. In certain circumstances, doses may vary, increasing them in cases of insufficient response and good tolerance or decreasing them in cases where tolerance is not adequate. Therefore, the dose decision is taken jointly by the treating medical team, considering the activity and toxicity presented in previous cycles, and it may be adjusted according to clinical criteria or need for treatment in both eyes. The number of cycles will depend on the response, being generally less than 4-6. Our group discourages prolonged attempts to conserve eyes with additional cycles of OAC in order to avoid increasing the risk of metastatic relapse[8].

INTRAVITREAL CHEMOTHERAPY

The technique for intravitreal injection is adapted from Munier et al[28]. Ultra-biomicroscopy (UBM), if available, is recommended in order to more accurately characterize the injection site. In most cases, the quadrant for injection can be easily identified with ophthalmologic examination, so the use of UBM would not be mandatory every time. However, in eyes with extensive vitreous seeding, especially when there is no response to chemotherapy, the use of UBM is preferred. Ultrasound examination is also recommended to assess the status of the hyaloid in order to avoid a subsequent injection behind it in case it had become detached. In all cases, a tumor-free quadrant of the retina is preferred in order to administer the drug safely. Paracentesis of the anterior chamber, taking up to 0.1 ml of aqueous humor is done at the beginning of the procedure by most groups. We prefer a fine needle, 32-34 G, although in some centers only 30 G needles are available as a smallest size. Since there are no randomized studies comparing the drug efficacy, we propose to use Topotecan (30 micrograms in 0.15 ml of saline) as initial treatment, based on its more favorable toxicity profile, especially in single eyes or those with good vision, reserving Melphalan (20 or 30 micrograms in 0.10-0.15 ml) for cases of incomplete response or relapse[29,30]. Both drugs can be previously prepared and stored in a freezer at -20C (with adequate temperature monitoring) since their stability has been reported[31,32]. Intravitreal injection is performed using a microscope, injecting the drug through the pars plana in the quadrant opposite the tumor lesion. Cryocoagulation is applied to the puncture tract to minimize the risk of seeding along the tract. Some groups additionally recommend shaking the eyeball and washing it with abundant distilled water to further minimize the risk of contamination, although reports and experimental studies show that it is a rare phenomenon[33,34]. There is controversy regarding the frequency of intravitreal chemotherapy applications from weekly injections to injections every 3-4 weeks. For this consensus, it was not given preference to any schedule, however, most participants agreed that in cases of massive vitreous seeding, especially in the form of a cloud, weekly application (at least in the first doses) might be advisable closely observing response and toxicity. It is recommended that the number of applications be a minimum of 2 for seeding in the form of dust, 3 for the form of spheres and 4 for the form of clouds, up to a (theoretical) maximum of 8 applications. It is also possible to apply an "induction" on a weekly basis and after observing a response, "consolidate" with 1 or 2 additional applications at 3 or 4 weeks. It is preferable that the tumor

is initially treated with OAC before intravitreal chemotherapy is administered. The results of intravitreal chemotherapy after systemic chemotherapy are not known.

SYSTEMIC CHEMOTHERAPY FOR LESS ADVANCED INTRAOCULAR TUMORS

Systemic chemotherapy for group B or C eyes is considered by most groups as standard treatment which may avoid the potential for ocular toxicity of OAC with a comparable success rate[35]. OAC may be used for relapse or incomplete response. However, patients with group B-C eyes with macular involvement benefit from the treatment with OAC[36]. In patients with unilateral group B-C retinoblastoma, we propose the indistinct use of systemic or OAC according to the experience of each group and local availability (favoring the use of OAC when available) in patients older than 6 months of age or over 6 kilos based on reports of shorter treatments and lower toxicity[37].

Although a study showed that two drugs (Vincristine and Carboplatin) are inferior to combinations with three drugs in the conservative treatment of retinoblastoma, our group decided to use the two-drug combination, without the use of Etoposide for patients receiving systemic chemoreduction[38]. The group agreed that the use of Etoposide is not justified in centers that have OAC since it has been associated with higher risk of secondary leukemias, even at doses considered safe in other neoplasms[39].

In patients with bilateral disease presenting with one eye group B or C and the contralateral eye group D (the most common presentation in our continent), the use of tandem OAC is also preferred as this would provide better chances of success in the treatment of the D eye. In cases of limited access to OAC or in groups with less experience in the use of tandem therapy, the use of systemic chemotherapy followed by OAC (+/- intravitreous chemotherapy) only for consolidation of the D eye may be an alternative.

MANAGEMENT OF PATIENTS WITH GROUP D SPORADIC UNILATERAL RETINOBLASTOMA

Considering the need for high utilization of resources and limited functional outcomes in unilateral eyes treated conservatively, we agreed that initial enucleation of most patients with sporadic unilateral disease with group D and all group E eyes is the standard treatment[40]. However, group D eyes includes many clinical situations from eyes with advanced disease with multiple vitreous seeding and low probability of useful vision, to eyes with smaller tumors, occasionally sparing the macula and presenting vitreous and/or subretinal seeding, in whom conservative treatment may preserve vision. Affected families may prefer conservative therapy and OAC should be offered when there is a reasonable chance of vision preservation[41]. It is important to consider that in our setting, it is seldom possible to have timely results of the presence of the germinal mutation of the RB1 gene so it can be considered in the initial therapeutic decision. Also, of note, we use the international classification of intraocular retinoblastoma in its original Murphree version[42]. Other groups use the Philadelphia modification where involvement of more than 2/3 of the retina is considered group E, rather to group D as in the Murphree classification[43]. No case with group E disease, according to the Murphree classification, will it be treated with conservative treatment in our setting.

MANAGEMENT OF PATIENTS UNDER 6 MONTHS OR 6 KILOS

In general, children under 6 months are not candidates for OAC, although this treatment may be possible in patients weighing more than 5 kg. Each situation will be assessed individually and in those that are considered to be ineligible to receive this treatment, a limited number of cycles of "bridge" systemic chemoreduction with single agent carboplatin (in a dose adapted to the age and gestational age) may be indicated until their weight makes them candidates for receiving OAC[44].

A summary of the treatment recommendations is presented in Table 3.

MANAGEMENT OF PATIENTS WITH BILATERAL RETINOBLASTOMA AND RISK FACTORS IN THE ENUCLEATED EYE

In patients with bilateral retinoblastoma and one eye of group E, in whom initial enucleation is indicated and conservative treatment with OAC of the contralateral eye is considered, the result of the pathology of the other eye should be awaited to indicate definitive treatment. In the event of pathology risk factors,

systemic chemotherapy will be indicated according to current recommendations or protocols in the GALOP group[40]. In case one or both eyes present with severe buphthalmos, we recommend neo-adjuvant systemic chemotherapy followed by secondary enucleation and systemic adjuvant therapy regardless of the HRPF[45]. If there is still active intraocular disease in the remaining eye, OAC may be used for secondary treatment.

CRITIQUE TO SELECTIVE OCULAR TREATMENTS

Lack of the "protective effect of systemic chemotherapy"

Retinoblastoma offers a period of "metastatic grace" when it is possible to give eye-conservative therapy with a low probability of metastatic dissemination[8]. The risk of metastatic relapse is restricted to patients with advanced intra-ocular disease who are usually not considered as candidates for eye salvage therapies and show pathologic risk factors. Recent studies suggest that retinoblastoma's biological subtypes may have different risk of metastasis and also patients with higher risk of metastasis show higher levels of circulating tumor DNA (ctDNA) at the moment of enucleation[46,47]. Hence, as OAC became more widely used for conservative therapy, some authors gave a word of caution for the putative loss of the "protective effect" of systemic chemotherapy to prevent metastatic dissemination[48]. Systemic chemotherapy is effective for the prevention of metastatic relapse in enucleated patients who present high risk pathology features, but this protective effect would not be needed in patients treated conservatively when adequately selected, because their risk of metastatic dissemination is minimal[40]. In fact, there are now more than 200 peer-reviewed papers in the past 15 years on survival after OAC and all reported a very low (<1%) risk of metastases in patients receiving this treatment, despite a low chemotherapy exposure in the systemic compartment[49]. In addition, OAC attains very high levels of chemotherapy to the optic nerve and choroid, giving enhanced "protection" to major sites of fatal retinoblastoma dissemination[50]. In fact, CNS relapse after OAC has been rarely reported and the few cases showing metastatic dissemination after OAC had systemic or orbital dissemination or in some cases, in middle income countries failed to comply with therapy[49]. The recognition that higher risk pathologic features exist before treatment and that enucleation does not prevent metastases in these eyes (as evidenced by the development of metastasis following enucleation) has spurred the use of eye and vision saving techniques even in eyes with some higher risk features in high income countries. [51] Our ability for non-invasively identifying patients at higher risk for developing metastatic disease or those with MYCN amplified tumors who are not candidates for eye salvaging is improving. Liquid biopsy studies reveal that patients who subsequently developed metastatic relapse had higher levels of ctDNA[47]. In these patients, ctDNA levels could be an indicator of higher tumor burden, and if ctDNA fails to disappear after enucleation it would show impending extraocular relapse in unilateral cases and in bilateral patients with controlled tumors. It may be possible that traditional treatment with initial enucleation in group E eyes may be challenged with these observations so that what was considered high risk pathologic features as prognostic indicators of risk of extraocular relapse would move to a more personalized management based on actual minimal dissemination to guide therapeutic decisions. This is also relevant for eyes that have received a high number of conservative treatments either local or systemic over a long period of time. In these patients, the "state of metastatic grace" may be lost and metastatic disease may develop.

Lack of protection for trilateral disease

Early results with the use of systemic chemotherapy suggested a possible effect in reducing the risk of trilateral disease in patients with germline *RB1* mutation[52]. However, they were based on a small number of cases and later studies failed to confirm this observation[4]. Subsequent studies revealed that the overall prevalence of trilateral retinoblastoma is lower after new and better designed studies were done and studies using OAC did not report an increased prevalence of trilateral retinoblastoma and the avoidance of EBRT by the use of OAC would further reduce its prevalence[53].

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