This paper was judged the BEST PAPER of PEDIATRIC OPHTHALMOLOGY Session.

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BEST PAPER OF PEDIATRIC OPHTHALMOLOGY SESSION

The Role of Subconjunctival Carboplatin in the Treatment of Advanced Cases of Retinoblastoma—A Series of First Ten Patients

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Retinoblastoma (RB) is the commonest primary intraocular malignancy in childhood with an incidence of 1 in 20000 live births.[1] Most of the patients are younger than 2 years and rarely tumors presenting at birth with systemic metastasis have also been described. RB may be multifocal or unifocal and involvement is usually asymmetrical in bilateral cases.[2] Patients with bilateral retinoblastoma have historically been treated with enucleation or external beam radiation therapy (EBRT) or both. Although the efficacy of ionizing radiation therapy has been demonstrated, this therapeutic modality is associated with complications such as facial deformities, cataract, and radiation retinopathy and an increased incidence of second tumors.[3] To avoid these radiation-related complications, systemic chemotherapy has become standard in the management of retinoblastoma.[4] However, systemic chemotherapy is associated with its own risks. The regimens currently used can cause neutropenia and infections, anaemia and thrombocytopenia that may require blood product transfusions, and organ toxicities including ototoxicity, renal toxicity, and hepatotoxicity.[5] In addition, although the precise risk of second nonocular tumors associated with the use of chemotherapy in early childhood in carriers of the *RB1* gene mutation remains to be determined, there is reason for concern.[5] These risks could potentially be minimized if locally administered chemotherapy could substitute for some of the systemic chemotherapy.

Antineoplastic effects of various agents have been observed after subconjunctival injection for intraocular epithelioma and ocular melanoma in the rabbit, intraocular lymphosarcoma in the cat, and ocular leukaemia in a human patient.[6-9] The rationale for using local chemotherapeutic injections is to increase the intraocular concentration of the agents, without incurring additional systemic toxicity from increasing intravenous dosages. It has been shown that intravitreal carboplatin is well-tolerated in nontumor-bearing primates and that higher levels of carboplatin are achieved in the vitreous humour when compared to levels achieved after intravenous administration.[10] Similarly, it has also been shown that intravitreal injections of melphalan in retinoblastomas with vitreous seeding achieved higher intravitreal levels which was important in achieving resolution of vitreous seeds in Stage V b disease and thereby achieving a success rate of 55.8% of eye preservation in the human eyes used.[11] Transgenic mice with retinoblastoma have also shown significant tumor control accompanied by little or no local toxicity using subconjunctivally injected carboplatin.[12, 13] The results of a phase I/II clinical trial of subconjunctival carboplatin in treatment of intraocular retinoblastoma found carboplatin to be effective as well as safe for use.[5] However, another study regarding the use of subconjunctival use of carboplatin in patients with recurrent and primary advanced

retinoblastoma did not show beneficial effect in recurrent vitreal or advanced primary retinoblastoma.[14] In the above light, we tried this therapy in one-eyed patients with advanced intra-ocular disease and vitreous seedings, in whom globe preservation was of paramount importance. We present our experience in the use of subconjunctival carboplatin in our first 11 patients.

Materials and Methods

This was a retrospective, nonrandomized comparative study with a concurrent control group. Retrospective analysis of the medical records of a group of 11 patients of retinoblastoma treated with subconjunctival carboplatin in our institute between 2001 and 2003 was performed. For the purposes of analysis, we chose a control cohort consisting of 11 randomly selected patients with retinoblastoma who were similar in all aspects (demography, Reese-Ellsworth staging[15] and treatment including systemic chemotherapy and local therapy) except for the use of subconjunctival carboplatin in the therapy protocol. A group of 10 consecutive patients of RB, presenting with similar demographic data and Reese-Ellsworth group, who did not receive subconjunctival carboplatin as a part of their treatment were also studied so as to serve as controls. Similar parameters were studied in the control group as well. The results obtained were compared between the study and the control group. The final outcome in terms of tumor regression or progression leading to need for enucleation and best corrected visual acuity at final visit were meticulously recorded and analysed. The statistical analysis was done by Fischer exact test.

Results

The study group had 11 patients of which 9 were males while 2 was female. There was a marked male predominance in the study group. The age range in the study group was 7 months to 6 years with the mean age being 3.57 years. The duration of symptomatology ranged from 1 month to 6 months with a median of 4 months. The disease was bilateral in all the cases All the patients in the study group had bilateral disease and, as we stated previously, all patients had Reese-Ellsworth Vb disease. The worse affected eye was already enucleated at the time of presentation in 8 cases and was enucleated at our institute, as the disease was progressing in those eyes despite therapy, in the remaining 3 cases. Thus, all the patients were essentially one-eyed patients and salvaging the eye was imperative in all of them. Similar was the case in the control group. All the patients in the study group received subconjunctival injections of carboplatin. A total of 54 injections were given in the study group (range 2-8 injections / patient, median of 5 injections). The subconjunctival injections of carboplatin were administered in a dose of 1.5 ml of 10 mg / ml solution every 3 weeks (Total = 15 mg). No serious complications were seen in any of the patients except for periorbital edema in 1 patient (case 3) that lasted for 4 days only. In the study group, 8 eyes (73%) showed good response to therapy in form of complete tumor regression after a median followup of 12.5 months with a range of 7-24 months; while 2 eyes (27%) had progression of the disease despite therapy and finally had to undergo enucleation. In the control group, only 2 eyes (18%) responded to therapy and showed tumor regression and 9 eyes (82%) showed progression of tumor despite therapy. Those 9 eyes were subsequently enucleated. This was in sharp contrast to the study group and was significant statistically ($p = 0.03$).

Discussion

Chemotherapeutic agents used in the present days include vincristine, etoposide, carboplatin, cyclophosphamide and cyclosporine-A. Cyclophosphamide and vincristine sulfate are among the more effective chemotherapeutic agents, but their use is associated with substantial toxicity that includes bone marrow suppression, nephrotoxicity, and myelotoxicity.[15] Platinum compounds such as cisplatin and carboplatin, demonstrate relatively low toxicity compared with other chemotherapeutic agents.[16] Clinical trials[17] have demonstrated the efficacy of systemic carboplatin therapy in the management of multiple pediatric malignancies (neuroblastoma, Ewing sarcoma, Wills tumor) and adult neoplasias as well. For these reasons, carboplatin is included in the chemothe-

rapeutic regimen for most patients with extraocular as well as intraocular retinoblastoma. The above have resulted in remarkably effective regression of intraocular retinoblastoma. As a consequence, such regimens now are used widely as primary chemoreduction therapy, especially in children who have bilateral retinoblastoma. These regimens need to be given under supervision by an oncologist who is familiar with the side effects and complications of the drugs. Chemotherapy is given as cyclical therapy every 3-4 weeks for at least 6 cycles. Systemic chemotherapy also is used to treat children who have extraocular tumor extension at presentation, orbital tumor recurrence after enucleation, intracranial extension of retinoblastoma, and metastasis.[18]

Carboplatin is an analogue of cisplatin that causes less toxicity and has been found beneficial in intraocular as well as extraocular retinoblastoma.[19] When administered intravenously, therapeutic levels of carboplatin enter the eye and bind firmly to tumor DNA where it forms platinum-DNA adducts. This DNA binding is the mechanism by which the drug kills tumor cells. Carboplatin has been found to be effective against brain tumors and is known to cross the blood-brain barrier.[20] Despite the relatively favourable toxicity profile for carboplatin, significant side effects have been observed including myelosuppression, nephrotoxicity, ototoxicity, sepsis, second tumors and death.[21] Ocular side effects of systemic carboplatin that have been reported include choroiditis, retinitis, maculopathy, optic neuritis, and optic neuropathy. Children with bilateral retinoblastoma have a strong genetic cancer diathesis and are at a greater risk for mutagenesis and second tumors. This has been shown clearly in previous reports when patients of retinoblastoma were treated with external beam radiotherapy or systemic chemotherapy.[22, 23] The above stated risks can be minimized if these modalities are replaced by chemotherapy delivered locally. We undertook the present study in order to evaluate whether subconjunctival carboplatin injections have any therapeutic benefit over and above systemic carboplatin or not. We studied 10 patients with retinoblastoma who received subconjunctival injections of carboplatin in addition to systemic chemotherapy and compared the results with a similar group of 10 patients who received systemic chemotherapy but did not receive subconjunctival carboplatin injections. The main outcome measures studied were tumor regression and final visual outcome. There is paucity of literature regarding the use of subconjunctival carboplatin. Although our study is a retrospective study, it has the benefit of having a control cohort for comparison of efficacy of subconjunctival carboplatin. Such a study has not been reported before. Harbour and coworkers[24] investigated the role of intravitreal injections of carboplatin in transgenic murine retinoblastoma and found that tumor development was inhibited by intravitreal injections of carboplatin in a dose-dependent manner. They calculated the dose of intravitreal carboplatin resulting in complete tumor cure in 50% of eyes (TCD_{50}) in their study to be 1.4 ìg. Murray and coworkers[12] published the results of their study conducted for evaluating the role of subconjunctival carboplatin therapy with or without cryotherapy in the treatment of transgenic murine retinoblastoma. They found a dose-dependent inhibition of intraocular tumor growth in their study with TCD_{50} being 180 ìg. They did not find any histopathological evidence of ocular toxicity. Hayden and coworkers[13] in another murine transgenic retinoblastoma model reported TCD_{50} of subconjunctival carboplatin to be 138.3 ìg for 10-week-old mice. Abramson and coworkers[5] were the first ones to conduct a phase I / II trial of subconjunctival carboplatin in intraocular retinoblastoma. They administered 1.4 – 2 ml of 10 mg / ml solution of carboplatin subconjunctivally and found good response to the therapy in tumors not associated with subretinal disease. The treatment was well-tolerated by most young children with intraocular retinoblastoma, with minor local toxicity and no clinically relevant systemic toxicity. This therapy was administered without any concurrent SALT therapy or systemic chemotherapy. However, only 54% of patients in their study group belonged to

group Vb whereas all the patients in our study (100%) belonged to group Vb. Also, all our patients were one-eyed. Thus, more advanced disease and need to preserve the only eye of the patient prevented us from stopping all other therapy to analyse the effect of subconjunctival carboplatin. Ghose and coworkers have also reported that subconjunctival carboplatin may have an adjuvant role in therapy for retinoblastoma.[25] However; their study was also a non-comparative case series and therefore could not substantiate the role of subconjunctival carboplatin. The various reported complications of subconjunctival carboplatin include periorbital edema, redness, optic atrophy[5] and ocular motility restriction.[26] The eye that developed optic atrophy had also been treated with cryotherapy and laser photocoagulation which might have been the causative factors. However in our study, no major side-effects developed in any of our patients. 1 case developed periorbital edema that resolved with cold compresses. This might be related to the fact that we administered the injections in a posterior subtenon's location in contradistinction to a subconjunctival anterior location. Thus, our study demonstrates the initial efficacy of subconjunctival carboplatin in the treatment of intraocular retinoblastoma. We especially recommend the use of this therapy in advanced disease. However, early cases may actually benefit more from this therapy as it might eradicate the need for concurrent use of SALT or/and systemic chemotherapy in these patients and avoid related morbidity and mortality. Further reports and prospective randomized clinical trials are necessary to substantiate the facts outlined in our study and to establish this modality of therapy firmly in the management of retinoblastoma.

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This paper was judged the BEST PAPER of SQUINT Session.

Effect of Silicon Band Spacing Technique in The Correction of Brown Syndrome

Dr. Elizabeth Joseph

The clinical entity known as Brown syndrome was described in 1949 by Harold Waley Brown as Superior Oblique tendon sheath syndrome. Most often it is a congenital anomaly of ocular motility but an iatrogenic form and acquired variety also occur. Classic congenital Brown Syndrome presents with inability to elevate the adducted eye actively and passively. However ,depending on the severity and the underlying etiology a number of other findings like elevation deficiency in midline, normal elevation in abduction, V pattern with divergence in upgaze restricted forced ductions, downshoot or hypotropia in adduction, widening of palpebral fissure in adduction, anomalous head posture, hypotropia in primary position etc. may be associated. Congenital brown syndrome is due to a primary abnormality in the SO tendon and or the tendon -sheath -trochlear complex which is present from birth The .different surgical procedures to correct browns syndrome like free tenotomy of SO, tenectomy, Sheathectomy, Z tenotomy and tendon recession, all remained unsatisfactory in most instances with gross undercorrection or secondary SO palsy. Wright introduced the technique of SO tendon lengthening with the insertion of a measured segment of silicon retinal band between the cut ends of tenotomised SO tendon to produce a controlled weakening. We have analysed the effect of Superior Oblique expander technique with the use of a silicon band in 12 eyes of 10 patients with classic congenital brown syndrome.

Materials and Methods

10 patients with congenital brown syndrome who underwent SO tendon lengthening