Original Article-I

Chemoreduction Helps Vision Preservation in Retinoblastoma

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ABSTRACT

Background: The role of chemotherapy in treating intraocular retinoblastoma (RB) has rapidly progressed since the last decade. With this approach enucleation or external beam radiotherapy can be avoided in selected cases of intraocular RB. Our study is a retrospective analysis of cases of intraocular retinoblastoma receiving primary chemotherapy and local therapy.

Methods: Newly diagnosed cases of intraocular RB were treated with primary chemotherapy followed by local therapy. Out of 75 cases that attended our institution during the period of 6 years from 1998 to 2003, 20 patients had intraocular disease and all of them received primary chemotherapy. 12 of 20 patients had unilateral disease, and 8 had bilateral disease. Reese- Ellsworth grouping was assigned to each of the diseased eye. A total of 28 eyes were treated with primary chemotherapy followed by local therapy.

Results: Among 28 eyes, vision could be preserved in 9 eyes (32%) while enucleation was carried out in 12 eyes (42.9%). Vision preservation was successful in the early stages (RE group I -III) of intraocular disease.

Conclusion: Use of chemotherapy followed by local therapy is effective in preserving vision in intraocular retinoblastoma especially in the early stages (Reese Ellsworth Group I -III).

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INTRODUCTION

Retinoblastoma (RB) is one of the most curable paediatric solid tumours. Effectiveness of chemotherapy in retinoblastoma was first demonstrated in extra ocular[1-3] and metastatic disease.[4] Experience prompted its use in intra ocular tumors as primary chemotherapy in an attempt to salvage vision wherever possible. The role of chemotherapy in treating intraocular has rapidly progressed since last decade.[6-11] This approach of chemo reduction has the potential of avoiding enucleation and / or external beam radiotherapy in selected cases of intra ocular RB thereby preserving vision.[12]

Retinoblastoma is fairly common in the north- eastern region of India. Our institute being the only regional cancer center in this part of the country, it caters to most of the patients in this region. But only a few cases present with early intra ocular disease and in those we have used chemo reduction followed by local therapy with an aim of preserving vision. Our experience with role of chemoreduction in vision preservation in patients with intraocular RB is the subject of this study.

METHODS AND MATERIALS

We carried out a retrospective analysis of all newly diagnosed cases of RB with intraocular disease who were offered primary chemotherapy. Between January 1998 and December 2003, 75 cases of RB were registered in our department. of these 20 patients had intra ocular disease and received primary chemotherapy followed by local therapy, 49 underwent primary enucleation while the remainder 6 presented with very advanced disease and received palliative radiation therapy only. Amongst 20 patients with intra ocular disease, 12 were male and 8 female children. Twelve of them had unilateral disease (age range-7 – 36 months, median age 26 months) and 8 had bilateral disease (age range – 0 – 26 months, median age 12months) (Table I). Therefore a total of 28 eyes were treated with primary chemotherapy followed by local treatments. All the patients underwent ophthalmological examination under anesthesia and Reese- Ellsworth Grouping (REG) [13] was assigned to each eye (Table I). Computerized tomography of the brain with cuts through the orbits was done in all the cases. The families of each patient underwent genetic counseling along with counseling regarding the treatment protocol and prognosis before commencing the therapy. All patients received 3 cycles of chemotherapy with carboplatin and etoposide (Table II). After 3 cycles of chemotherapy patients were re-evaluated by ophthalmologist regarding response to chemotherapy. In eight cases they received one more cycle of chemotherapy. After completion of chemotherapy each eye was re-evaluated by ophthalmological examination and then subjected to local therapy in the form of cryosurgery, photocoagulation, thermo- therapy or external beam radiotherapy (EBRT).

RESULTS

Of the total 20 patients that were considered for chemoreduction followed by local therapy, 12 presented with unilateral disease while 8 had bilateral disease. Two patients with bilateral disease had a positive family history of RB and amongst them one patient's mother was a case of unilateral RB who was also treated in our institute earlier. Vision preservation was successful in 9 eyes (32%), 12 (42.9%) had unilateral enucleation while 3 were lost to follow-up after 2 cycles of chemotherapy, 2 received EBRT and 2 had progressive disease. There was no major toxicity following chemotherapy except for transient bone marrow suppression in 4 patients (20%) requiring transfusion. Out of 20 patients 9 (45%) patients are on follow-up till date and 4 had completed 5 years follow-up.

Table -I Age groups of unilateral and bilateral disease

Disease	Total Cases	Age range in months	REG I-III	REG IV-V
Unilateral	12	7-36	4	8
Bilateral	8	0-26	7	1

REG : Reese-Ellsworth Grouping

Unilateral disease (Figure I): All the 4 patients with RE group I to III received three cycles of chemotherapy followed by cryosurgery (1 session) or photocoagulation (2-3 sessions) and vision was preserved in all the four patients. In the patients with RE group IV to V, only one patient's eye could be preserved with useful vision, five underwent enucleation and two received external beam radiotherapy.

TABLE : II Chemotherapy Schedule

Drugs	Weight	Dose (per sq mt)	Duration
Carboplatin	>10kg	200mg	D1 – D3
Carboplatin	<10kg	6.7mg	D1 – D3
Etoposide	>10kg	150mg	D1 – D3
Etoposide	<10kg	5mg	D1 – D3

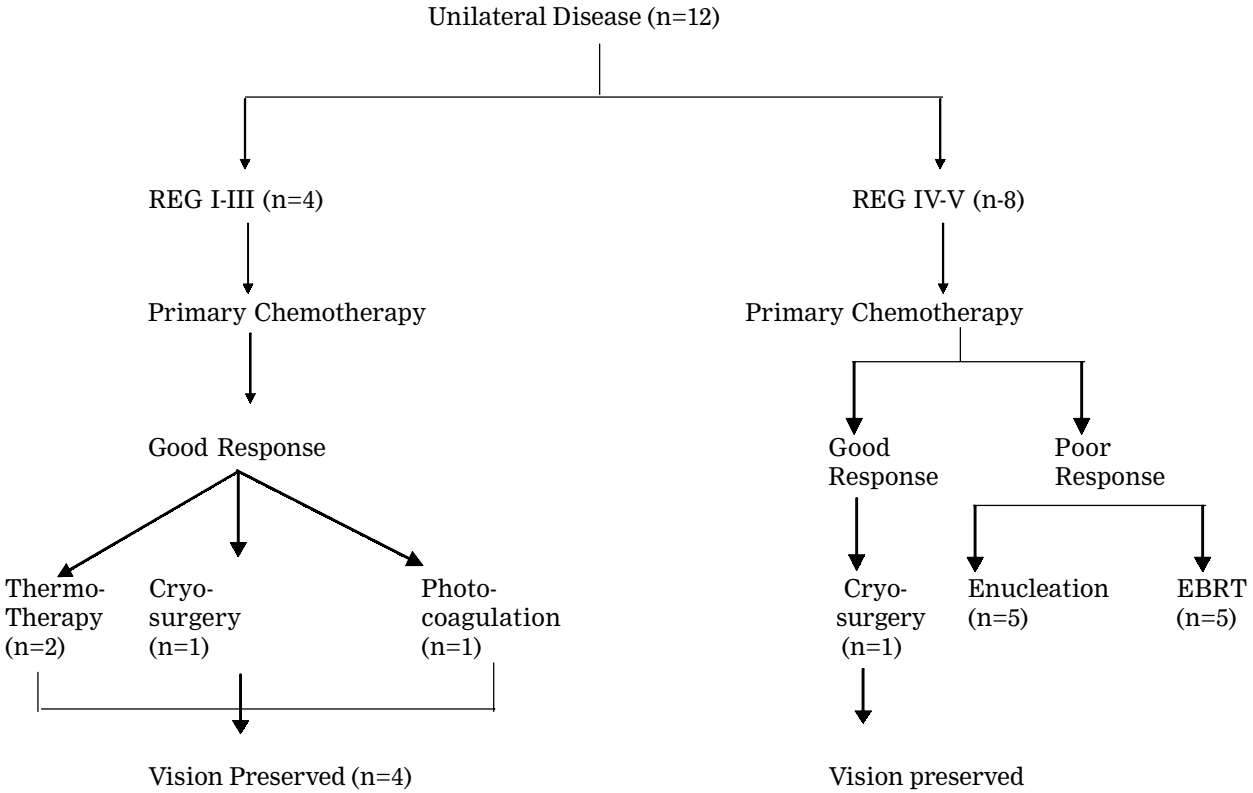

FIGURE I

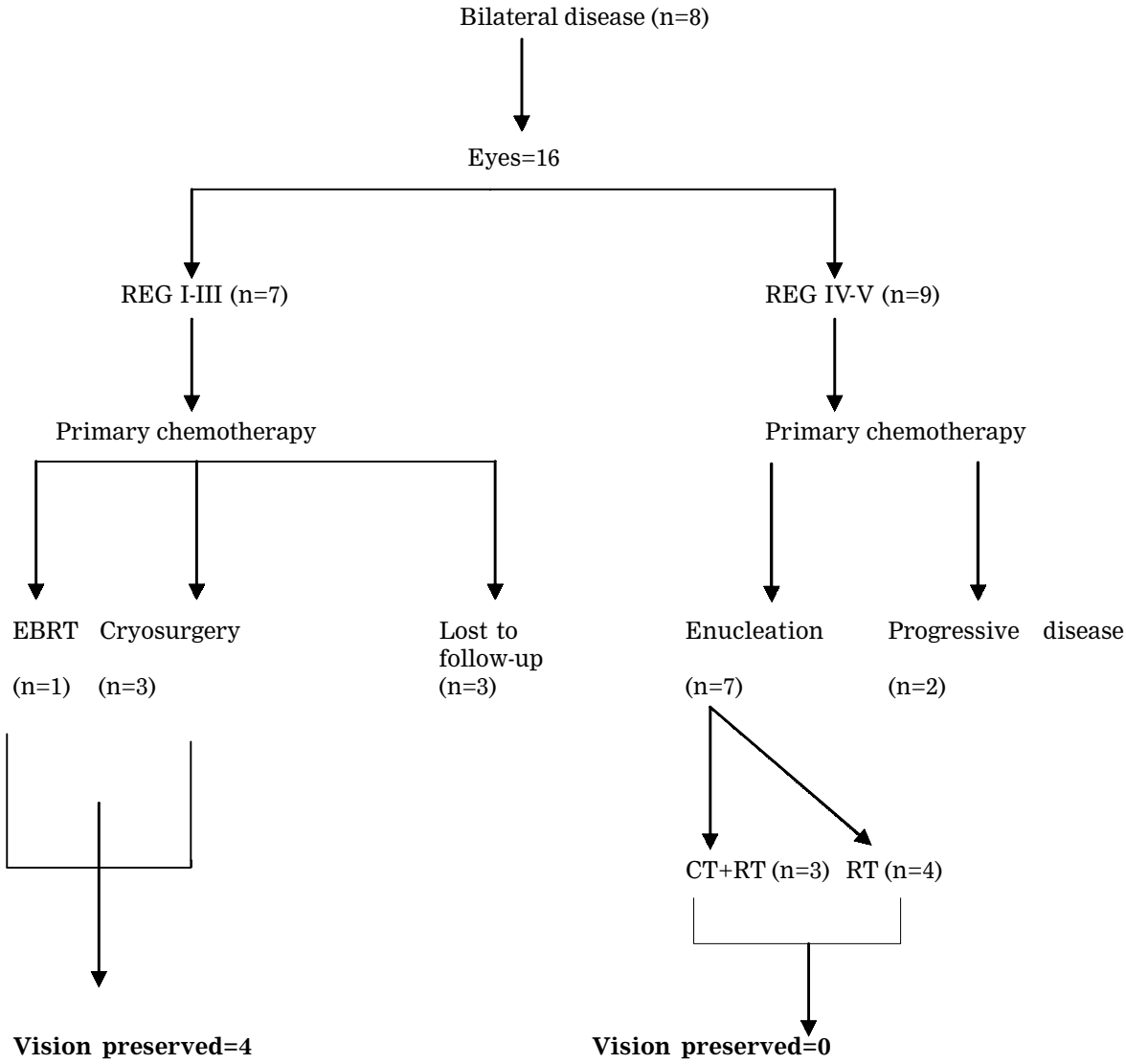

FIGURE II

Bilateral disease (Figure II): In case of bilateral disease, since there were 8 patients 16 eyes were involved. Out of these 16 eyes 7 were in RE group I - III and the rest 9 in RE group IV - V. Of the 7 eyes with RE group I - III vision could be preserved in 4 eyes while in the eyes with RE group IV-V tumours vision preservation was unsuccessful. Of the 9 eyes with RE group IV-V disease 7 underwent enucleation as there was no useful vision at diagnosis and also there was partial response to chemotherapy. The rest 2 cases had progressive disease.

DISCUSSION

In developing countries retinoblastoma presents more frequently with advanced disease probably as a consequence of delayed diagnosis.[16] In our study also among 75 patients only 20 patients presented with intraocular disease in whom cytoreduction was considered in an attempt to preserve vision. Even then vision preservation could be done only in nine eyes (32%). In our study RE group I to group III tumour showed good response to chemotherapy where vision preservation could be considered. Murphree et al also reported the use of chemoreduction plus SALT (sequential aggressive local therapy) as primary treatment in 35 eyes and was successful in 10 eyes with group I and IV tumours.[7]

The 5 years survival rate of retinoblastoma now exceeds 90%.[14] Therefore the emphasis is on eradication of disease with preservation of useful vision. Current studies completed by the Retinoblastoma Study Group show the promising use of primary chemotherapy in reducing tumor bulk followed by various forms of local therapies.[15] Primary chemotherapy or cytoreduction has been the most significant advance in the treatment of retinoblastoma. This is typically the principal mode of treatment for intraocular tumours.[15]

One major bias in our study is the lack of prospective design of local therapy. Moreover due to non-availability of brachytherapy plaques, a few patients had to receive external beam radiation therapy. Even though in our study external beam radiation therapy has to be given to quite a few numbers of patients with less advance disease, chemoreduction helped to delay its administration. Abramson and Frank reported that the cumulative incidence of second primary malignancy correlates with the age at radiotherapy. Patients that received external beam radiation therapy during their first year of life may have a higher cumulative risk of developing secondary cancers within the radiation field than those radiated later in life.[17] Another concern was about using etoposide and the risk of secondary leukemia. The dose and schedule of etoposide seem to be important for developing secondary malignancies.[18] A recent report from the secondary leukemia-monitoring plan of the Cancer Therapy Evaluation Program of the National Cancer Institute suggests that a cumulative dose of 5g/m2 given on a daily schedule for five consecutive days does not significantly increase the risk of secondary leukemia above that contributed by other agents.[19] In our study patients received 3 to 4 courses of chemotherapy for a cumulative dose of 1.8 to 2.4g/m2, therefore the treatment regime is considered to be safe with regard to secondary leukemia.

The use of chemoreduction and local therapy in intraocular retinoblastoma resulted in better eye preservation and less use of radiotherapy.[20] Due to limited availability of sophisticated local therapy in developing countries sometimes external beam radiation therapy may have to be used even in less advanced disease.[20]

In conclusion, our retrospective study showed that this strategy of chemoreduction followed by local treatment is an effective tool towards vision preservation in cases of intraocular retinoblastoma especially in RE group I to III tumours.

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