Outcome of Primary Orbital Retinoblastoma Managed by Intensive Multimodal Treatment Protocol

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Retinoblastoma (RB) though a rare malignancy in the general population, the outcome can be fatal if not managed appropriately. In the recent past the advancement in the management of intraocular retinoblastoma has been soaring heights, with an aim of vision salvage, eye and life salvage. With the current available treatments and early diagnosis most of the patients are benefited. However, advanced diseases like orbital RB is still a matter of concern, more so in the developing world. Orbital RB is the prime determinant factor of metastasis and death, with 10-27 times higher risk of metastasis.\(^1\)\(^3\)

The disease is rare in developed countries with a relative decline from 6% to 2%.\(^4\) However in the developing countries of Asia, Africa and Central America it is as high as 30-60%.\(^5\)\(^\)\(^13\) Needless to say the scenario is dismal. Infact, lack of awareness, socioeconomic constraints and inaccessibility to optimal medical care plays a major role.\(^14\) Apart from all, we also fall short in offering a protocol based intensive management for an advanced disease where it has disseminated beyond the confines of the eyeball. Due to the widespread disease locally and possible systemic micrometastasis, it invariably carries a grim prognosis with mortality rate as high as 90-100% with conventional management.\(^14\)\(^\)\(^15\)

As reported by Hungerford et. al. in his series, the only survivor, received additional chemotherapy.\(^16\) It was Ellsworth in 1974, who first recommended and highlighted that systemic chemotherapy improved the survival in patients with Orbital RB.\(^17\) Few other authors with combination of multiagent chemotherapy, exenteration and radiotherapy have subsequently challenged the dismal outcome of Orbital RB, improving the survival rate to 75- 85%.\(^19\)\(^\)\(^25\) The logical approach thereby in Orbital retinoblastoma would be judicious and sequential combination of neo-adjuvant chemotherapy, followed by surgery, external beam radiotherapy (EBRT) for local disease control and extended chemotherapy in the form of adjuvant therapy to control systemic micrometastasis- Sandwich Chemotherapy.
MATERIALS AND METHODS

We retrospectively analyzed the records of all patients diagnosed as Orbital Retinoblastoma (RB) who were included in the prospective intensive multimodal treatment protocol (IMTP) from January 2000- December 2010 at Ocular Oncology Services in a tertiary eye care center in India. Those patients with regional lymph node metastasis and systemic metastasis at initial presentation along with those with follow-up less than six months were excluded from the study. The study was approved by the institutional review board and informed consent was taken from parents and guardians.

The retrospective data analyzed constituted, demographic profile including patient age at diagnosis (in months), gender, hereditary pattern (familial/sporadic), laterality of involvement and the involved eye. The clinical features, metastatic work up (cerebro-spinal fluid (CSF) cytology, bone marrow (BM) biopsy and lymph node biopsy if clinically palpable) done at the initial as well as the subsequent visits were analyzed in detail. Computerized tomography (CT) imaging reports were reviewed. Operative notes were reviewed in detail for extra ocular extension and optic nerve extension and resected optic nerve stump length. Histopathological reports were evaluated for the evidence of full thickness scleral invasion, extrascleral extension and involvement of optic nerve transection. Primary orbital RB were further classified as anterior, mid, posterior and diffuse depending on the radiological location and extent as noted.

Intensive Multimodal Treatment Protocol (IMTP)

The triple drug chemotherapy regimen was followed in all patients, which included Vincristine, Etoposide and Carboplatin (VEC). The protocol included, commencing the treatment with high dose chemotherapy (VEC), 3 to 6 cycles followed by enucleation after radiological confirmation of complete regression of the orbital tumor, further augmented with EBRT, 2 weeks following surgery. The EBRT dosage ranged from 3000-4500 cGy. The treatment was consolidated with extended high dose adjuvant chemotherapy and completion of 12 cycles. All patients underwent computerized tomography (CT) imaging before commencing the first cycle of chemotherapy and repeated after every third cycle prior to surgical management. Baseline metastatic work up was done in all cases. Information regarding the outcome included occurrence of metastasis, date of detection of metastasis, interval between enucleation and detection of metastasis (months), and the site of metastasis. The final patient outcome (alive without metastasis, alive with metastasis, alive with second malignant neoplasm, dead with metastasis, death with second malignant neoplasm, or death due to other causes), the date of last follow-up, and the duration of follow-up were noted.
Complications of chemotherapy and EBRT were analyzed. On subsequent follow up at 3, 6, 12, 18, 24 and 36 months, complete clinical evaluation was done. CT imaging was requested at 12, 18, 24 and 36 months to rule out orbital recurrence. Systemic metastatic work-up was performed at 6, 12, 18, 24 and 36 months.

**Statistical analysis**

The clinical data was analyzed with respect to the main outcome measures, metastasis and death. The effect of each individual demographic factor, clinical variable and treatment modality on the final outcome was analyzed. For categorical variables, Chi-square test or Fischer Exact test were used and Mann-Whitney test was done for continuous variable. The event-free survival curves at 100 months were calculated according to Kaplan–Meier analysis and the curve comparison was done with the log-rank test.

**RESULTS**

Of the 1067 patients with Retinoblastoma (RB) managed at the oncology clinic from January 2000- December 2010, 124 patients presented with advanced retinoblastoma including those with orbital RB. Out of the forty eyes with orbital retinoblastoma, 20 eyes of twenty patients were classified as primary orbital retinoblastoma and, included in the study.

The mean age was 53 (range, 12 to 288 months; median, 35) months. There were 13 males (67%) and 7 females (35%) and, all patients except one were sporadic in presentation. Orbital retinoblastoma was unilateral in all the patients. They presented with proptosis (n=14, 70%), orbital cellulitis (n=2, 10%), secondary glaucoma (n=1, 5%), buphthalmos (n=1, 5%) and phthisis bulbi (n=1, 5%). Orbital extension was radiologically classified as, anterior (n=1, 5%), middle (n=2, 10%), posterior (n=9, 45%) and diffuse (n=5, 25%).

Three patients (15%) had optic nerve extension without orbital soft tissue involvement. However, optic nerve extension was noticed in 19 eyes (95%).

All the patients underwent high-dose chemotherapy (vincristine, etoposide and carboplatin (VEC) with median 12 (mean 11.9±0.4) cycles. All eyes underwent enucleation except for one patient in whom exenteration was performed due to non-regression of tumor after nine cycles of neoadjuvant chemotherapy. Sandwich external beam radiotherapy (linear accelerator) was performed in 17 eyes at a dose ranging from 3900-4480 cGy, median 4200 (mean 4194±155.8) cGy.

There were no permanent complications of systemic chemotherapy except for sixteen patients who had anemia and pancytopenia, which was successfully treated with whole blood and platelet transfusion and, granulocyte colony stimulating factor (G-CSF). All sockets were assessed
and, contracted socket was diagnosed in two patients, one of the sockets underwent fornix formation sutures and dermis fat graft; prosthetic revision was attempted in the other with relatively good cosmesis.

All the patients with orbital retinoblastoma were followed up for a minimum of six months. The median follow up was 74 months (range, 6 to 143; mean, 73±42 months). Overall survival in 20 patients on completion of IMTP was 90%. Central nervous system metastasis developed in two patients (10%) at a median follow up of 9.7 months. Both the patients had presented with primary diffuse orbital retinoblastoma with optic nerve extension upto the apex. One of the patients was noncompliant to treatment for intraocular retinoblastoma and was lost to follow up to return with massive extraocular extension. Infact the same patient underwent exenteration for non-regression of the orbital tumor. Palliative treatment was administered in the form of five cycles of intrathecal methotrexate (6mg) and triple drug (methotrexate, cytarabine and dexamethasone) in the same patient. Both the patients succumbed to death at 1.5 months and 2.5 months after completion of treatment respectively. Kaplan-Meyer analysis revealed 90% survival at the end of 5 years.

**DISCUSSION**

With the advent of newer therapeutic modalities, the survival of patients with retinoblastoma has gradually improved. Most of the children benefit from the current management options, which includes laser photocoagulation, cryotherapy, chemo reduction, external beam radiotherapy, plaque brachytherapy and the most recent intra-arterial chemotherapy. Advanced disease with extraocular extension breaching the confines of eyeball, has poor prognosis with local and systemic dissemination. Orbital retinoblastoma is the leading cause of disease related death worldwide due to metastasis, remarkably so in the developing countries. The mortality rate ranges from 94%-100% and a mean survival of 14 months.\(^{15-17}\) Inspite of this dismal scenario there are very few studies to provide evidence to treatment outcome since it is a rare entity as compared to other pediatric tumors. Nevertheless there is a need of a protocol-based management in such dreadful disease as in any other malignant pediatric tumors.

During the last few decades it was clearly evident in various studies, that multimodal treatment approach in common cancers like breast carcinoma and small cell carcinoma of the lungs has improved the survival rate to more than 95%.\(^{26}\) Thereby, the logical approach to treat orbital retinoblastoma would be judicious and sequential combination of escalated dose of chemotherapy, enucleation and radiotherapy with consolidation chemotherapy. It was Ellsworth in 1974, who for the first time strongly
suggested that aggressive treatment with combined chemotherapy and radiotherapy improved the survival in orbital retinoblastoma.\textsuperscript{17} Similarly, Goble and associates in 1990 in their case series of five secondary orbital retinoblastoma, reported 100\% survival with combination of tumor excision, multidrug chemotherapy and radiotherapy compared to 100\% mortality in nine patients who was treated with only exenteration and radiotherapy.\textsuperscript{19} In the Hungerford series of 16 patients all patients who were treated with exenteration and chemotherapy alone or in combination died, except for the patient who received a combination of additional chemotherapy.\textsuperscript{20} This highlights the fact, that micro metastasis proves to be the leading cause of death despite local control of the tumor.

Orbital retinoblastoma is a unilateral disease, usually presenting in older children. In our series the median age of presentation was 35 months and unilateral in all, in concordance with previous studies.\textsuperscript{1,3,4,14,25} Orbital invasion occurs generally via ocular coats, scleral emissary and optic nerve. The classification that we adopted was the clinicopathological classification proposed by Honavar \textit{et. al.}

Various authors challenged the dismal outcome of orbital retinoblastoma with combination of chemotherapy, surgery and radiotherapy. Several modifications in the treatment regime have been tried in the past.\textsuperscript{27} Doz \textit{et. al.} reported their results on the outcome of orbital retinoblastoma in 33 patients treated with combinations of systemic and intrathecal chemotherapy, orbital and CNS irradiation with 34\% survival.\textsuperscript{21} At 22 months of median follow up, out of the sixteen patients with massive orbital retinoblastoma as reported by Kiratli \textit{et. al.}, twelve patients (75\%) survived with combination of surgery, chemotherapy and radiotherapy. This case series highlights the other side of the spectrum where chemotherapy and external beam radiotherapy alone improved survival even in the presence of CNS metastasis.\textsuperscript{22} Pratt \textit{et. al.} advocated the role of multiagent chemotherapy with a reported survival rate of 70\%.\textsuperscript{18} Similarly, Antonelli \textit{et. al.} reported a survival rate of 65.3\% in the first group of orbital RB (including microscopic involvement of scleral emissaries and cut end of optic nerve) patients who were treated with multiagent chemotherapy including cisplatin, tenoposide, doxorubicin, cyclophosphamide and vincristine, and 75.5\% in those who were treated with ifosfamide, etoposide and cisplatin. The survival rate between the two groups with combination radiotherapy showed no statistical significance. However, chemotherapy was administered only as induction therapy of three cycles before undergoing enucleation, no patients received adjuvant chemotherapy.\textsuperscript{28}

Chantada and associates treated fifteen patients with neoadjuvant
chemotherapy followed by enucleation and orbital radiotherapy (4500 cGy) augmented with adjuvant chemotherapy. They reported an encouraging survival rate of 85%, though the total number of chemotherapy cycles was not mentioned.

In our study, the multimodal treatment protocol showed encouraging results in patients with orbital retinoblastoma with overall 90% survival rate. The two patients who died were diffuse primary orbital RB with optic nerve extension. One patient had undergone six cycles of chemoreduction for bilateral ICIOR group D tumor. The presumed reason for treatment failure could be chemo resistance.

The triple drug regime in our study included carboplatin that has high penetration into central nervous system and bone marrow, improving survival. Etoposide and carboplatin is found to act synergistically when combined. However escalating the doses also is useful in increasing the concentration of chemotherapeutic agents in the systemic circulation providing additional benefit. Complications related to systemic chemotherapy were transient and was intervened successfully by pediatric oncologist. Chantada et. al. in their series of 26 patients, though they had an overall survival of 70% in patient with invasion of cut end of optic nerve, 3 patients succumbed to secondary malignancies including acute myeloid leukemia. None of our patients received cranial radiotherapy. We do not recommend enucleation in orbital RB, which can grossly affect the cosmesis of a growing child. Contracted socket as a result of radiotherapy was seen in two of our patients. But, recent advancement in radiotherapy, and adopting the technique of Intensity modulated radiation therapy; such complications were avoided in subsequent children. Conclusion:

In this retrospective analysis of a prospective interventional study, we recommend intensive protocol based multimodal therapy in patients with orbital retinoblastoma. Kaplan-Meyer survival curve showed 90% at the end of 5 years. Our study has all the limitation of a retrospective analysis, but conducting a large randomized trial in a single centre on such advanced disease that is fortunately very rare is difficult. A multicenter trial can throw more light to the un-answered issues associated. However, from our experience from this study, we suggest that multimodal protocol based management with high dose chemotherapy combined with enucleation and radiotherapy offers improved survival in children with orbital retinoblastoma. Despite the treatment being effective and satisfactory, cutting edge research can identify better therapeutic agents for combating drug resistance and reducing toxicity. After all prevention is always better than cure, public awareness and improving the existing infrastructure in identifying and treating high-risk cases in the early stage may help us combat this dreadful pediatric cancer.
REFERENCES


