OUTCOME OF CHILDREN WITH RETINOBLASTOMA TREATED WITH PRIMARY CHEMOTHERAPY

Tariq Muhammad Saeed¹, Zafar Iqbal² ³ ⁴

ABSTRACT

OBJECTIVE: To study the outcome of children with retinoblastoma treated with primary chemotherapy.

METHODS: This was a hospital-based cohort prospective study of 91 children with retinoblastoma out of which 27 children (32 eyes) fulfilled the inclusion criteria. These children were admitted to Ophthalmology Unit, Lady Reading Hospital, Peshawar, Pakistan during the period of 1st January 2011 to 31st December 2013. Diagnosis was established by compatible history and ultrasonographic demonstration of posterior chamber mass with calcification. CT-Scan aided in diagnosis and also excluded extra scleral/intracranial extension. Examination under anesthesia allowed classifying the tumor according to Reese-Ellsworth classification system. Children of consenting parents were started on primary chemotherapy. Secondary treatment consisted of cryotherapy and/or argon laser photocoagulation.

RESULTS: The mean age of the cohort was 2.35 years. A total of 72% had advance stage IV or V disease. Secondary treatment was given in 43% eyes, whereas, 57% needed to be enucleated. Chemoreduction salvaged 43% of the eyes. The mean survival in the cohort was 67.88 weeks and the Kaplan Meier cumulative 2 year survival rate is 77%. Primary chemotherapy improved survival in the cohort (none died). The test statistic (log rank is 20.04 (df-1); p<0.001). But, was not attributed to preventing globe loss (x² = 2.52 (df-1), p=0.112). Preventing globe loss was attributed to the stage of the disease at time of diagnosis (x² = 11.476 (df-1), p<0.001).

CONCLUSION: Primary chemotherapy improves survival but not globe salvage in children with retinoblastoma. Invariably, the deciding variable for vision and globe salvage is the stage of disease at diagnosis.

KEY WORDS: Retinal Neoplasms (MeSH); Eye Neoplasms (MeSH); Retinoblastoma (MeSH); Chemotherapy (MeSH); Cryotherapy (MeSH).


INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy of the developing retina in children representing approximately 4% of childhood cancers and less than 1% of all human cancers. It may affect either eye and has no gender, racial or geographical predilections.

Retinoblastoma is 60-70% unilateral and most are non-hereditary (median age at diagnosis is 2 years). Retinoblastoma is bilateral in 30 - 40% of cases (median age at diagnosis is 1 year). This represents mainly hereditary retinoblastoma. The frequency varies from country to country and is between 1 in 15000 to 1 in 20000 live births. Approximately, 260 cases are newly diagnosed each year in Pakistan, and worldwide estimates are up to 8000 yearly.

Leukocoria is the most frequent sign (60%) and is associated with retinoblastoma in almost half of all infants presenting with a white pupil. Calcium complexed with denatured DNA is a histological hallmark, which can be easily detected by an ophthalmic ultrasound in the outpatient department. Examination under anesthesia allows visual confirmation of diagnosis and helps in charting treatment.

The treatment of retinoblastoma has evolved over the years. Previously enucleation was done to save the life of the child. Now treatment concentrates not on only life but also salvaging the globe and vision of the child. Primary chemotherapy has been increasingly used in the treatment of intraocular retinoblastoma. It has provided an opportunity for tumor shrinkage (chemoreduction) and thus, a chance to use adjuvant treatment modalities such as cryotherapy and argon laser photocoagulation. This has resulted in better survival with vision and globe salvage.

The study was performed to assess the response to primary chemotherapy and its effect on survival for children with retinoblastoma. Also the study aimed to ascertain variables contributing to globe salvage.

METHODS

This was a hospital-based cohort prospective study of 91 children with retinoblastoma out of which 27 children (32 eyes) fulfilled the inclusion criteria. These children were admitted to Ophthalmology Unit, Lady Reading Hospital, Peshawar, Pakistan during the period of 1st January 2011 to 31st December 2013. Diagnosis was established by compatible history and ultrasonographic demonstration of posterior chamber mass with calcification. CT-Scan aided in diagnosis and also excluded extra scleral/intracranial extension. Examination under anesthesia allowed classifying the tumor according to Reese-Ellsworth classification system. Children of consenting parents were started on primary chemotherapy. Secondary treatment consisted of cryotherapy and/or argon laser photocoagulation.

REFERENCE

1. Ophthalmology Ward, Saidu Teaching Hospital, Saidu Sharif, Swat, Pakistan
Email: tarik_saeed@yahoo.com
Contact #: +92-3339131288, +92-3329293129

2. Department of Ophthalmology, Medical Teaching Institute Lady Reading Hospital, Peshawar, Pakistan.
Email: dr_ziqbal@yahoo.com
Contact #: +92-3339131288, +92-3009595976

Date Submitted: February 02, 2018
Date Last Revised: March 18, 2019
Date Accepted: March 19, 2019
Secondary treatment consisted of photocoagulation, enucleation, cryotherapy, and argon laser photocoagulation. Each child consisting of chemotherapy primarily in liaison with an oncologist. An intravenous cocktail of Vincristine 1.5 mg/m², Carboplatin 560mg/m² and Etoposide 150mg/m² was given on DAY 0 and Etoposide 150mg/m² on DAY 1. Secondary treatment was decided according to response to chemotherapy. Each child was reviewed after 2⁴, before 5⁰ and after 6⁶ cycles of chemotherapy, which were given 3-4 weeks apart. Secondary treatment consisted of cryotherapy, argon laser photocoagulation, enucleation, and palliative therapy.

Argon photocoagulation was performed under general anesthesia for posteriorly located tumors using an indirect ophthalmoscope mounted on an argon laser (Quantel Medical Argon laser with Keelar indirect ophthalmoscope). Using a 20 diopter lens, the entire surface and surroundings of the tumor were coagulated with a laser intensity increased from 300 milliwatt and 0.2 second duration till the achievement of a clearly visible white mark. These laser marks were overlapped to cover the tumor. Cryotherapy using a triple-freeze-thaw method via transconjunctival route was done for anteriorly located tumors and also for posterior tumors through a conjunctival peritomy. Cryotherapy was performed before the 5¹ cycle after chemoreduction was achieved. Additional cryotherapy was performed after the 6⁶ and subsequently whenever typical regression pattern was not observed or there was evidence of regrowth at specified followup schedules. Each focal therapy was followed by two additional chemotherapy cycles and a review. A maximum of 12 cycles of chemotherapy were set as the upper limit. Enucleation was performed when tumor was found to be chemo-resistant after a minimum of two cycles of chemotherapy. Treatment failure was defined as chemo-resistance (progression in size) after a minimum of two cycles of chemotherapy, initial response and then relapse and the development of vitreous, subretinal or anterior chamber seeds.

Epidemiology and end results were statistically analyzed using SPSS version 10. The cumulative survival rate was calculated by the Kaplan-Meier method. Chi square analysis of outcome variables e.g. primary chemotherapy, staging of tumors and end outcome of treatment was done.

**RESULTS**

The cohort consisted of 27 children, 22 unilateral and 5 bilaterally affected (32 eyes) with a mean age of 2.35 years. Majority of the children presented with advance stage IV and V disease i.e. 72% (23 of 32 eyes).

Chemotherapy was offered to each child as a primary treatment of which 24 consented to the treatment protocol. Two children opted for primary enucleation and 1 for primary enucleation, all unilaterally affected. These three children neither received any chemotherapy before or after the primary treatment due to non-compliance of parents with treatment protocol. All three children eventually died, with a mean survival of 29.67 weeks. One child unilaterally affected received 4 cycles of chemotherapy, was lost to follow-up and dropped out of the study.

The cohort for secondary treatment thus consisted of 23 children (28 eyes). Secondary treatment consisted of chemotherapy plus adjuvant focal therapy (cryotherapy &/or argon photocoagulation) in 12 (43%) eyes and enucleation in 16 (57%) eyes. Invariably, those eyes in which tumors responded to chemoreduction were salvaged (43%).

The mean survival in the cohort was 67.88 weeks and the Kaplan Meier cumulative 2 year survival rate is 77% (Figure 1). Primary chemotherapy improved survival with a test statistic of 20.4 (df =...
In a previous study in the same unit, eyes with advance disease (stage IV and V) with no prospect of useful vision were not eligible for conservative treatment. Consequently, 94% of unilateral and 27% of bilaterally affected eyes were enucleated. In 2011, following the changing trends in the treatment strategy for retinoblastoma, every child admitted to Ophthalmology Unit, Lady Reading Hospital, Peshawar, Pakistan was started on primary chemotherapy. The rationale was to defer enucleation so as to assess tumor response to chemoreduction which would offer a cure in some cases. In cases where a cure was not achieved, chemoreduction would at least allow sufficient time for parents to settle with the idea of their child losing an eye. Children refusing primary chemotherapy and those with overt extracocular disease were managed surgically. With time, tumors with different stages of regression were seen. Some tumors regressed completely, whereas, others reduced to a size where complimentary cryotherapy and/or argon photocoagulation could afford globe salvage.

Out of 27 children (32 eyes) in the cohort, 24 children were started on primary chemotherapy all of whom survived the study. Two children opted for primary exenteration and one primary enucleation. None of these children received chemotherapy either before or after the primary treatment because of non-compliance of the parents with the treatment regimen. All three eventually died, with a mean survival of 29.67 weeks. Primary chemotherapy improved survival with a test statistic of 20.4 (df–1), p < 0.001. Generally, the more chemotherapy a child received better was the survival. A weak positive correlation was established with an R value of 0.434 (r2 = 0.189). A similar improved survival was reported by Waddell KM. He reports 37% lower risk of dying in 181 treated eyes compared to 89 after the introduction of chemotherapy into their treatment protocol in 2009.17

Primary chemotherapy was well tolerated and improved survival without complications but was contributing to globe salvage. A total of 29 of 32 eyes received primary chemotherapy. One child, unilaterally affected, was lost to follow-up after receiving 4 cycles of chemotherapy. The cohort now consisted of 28 eyes of which 16 eyes were lost (57%). Only 12 of 28 eyes (43%), globes were salvaged. Primary chemotherapy did not contribute statistically to globe salvage, (x2 = 2.52 (df–1), p = 0.112). In the absence of chemotherapy, the remaining 12 globes would have been lost. A better statement would be that chemotherapy salvaged those eyes in which tumors were chemosensitive and detected early. Studies have shown that chemotherapy alone has resulted in tumor control rates for Reese-Ellsworth (R-E) group I-IV of 51-86% and 25-38% in advanced tumors (R-E group V).18-19 When combined with focal laser consolidation the control rates increase to 62-100% and 47-83% respectively.20-21 Similarly, Bechrakis NE, et al.22 observes that primary chemotherapy is not equally effective in all children and advocates careful observation and consolidation with ancillary treatment.

In this study, we attempted to determine the effect of different treatment variables for globe salvage. One such variable was the number of chemotherapy cycles up to enucleation. Nine out of twenty eight eyes received < 6 cycles of chemotherapy during the treatment regimen. Six of these eyes (66.7%) were lost. Nineteen of twenty eight eyes received > 6 cycles. Ten of the eyes in this group were lost (52.6%). About half of the eyes (16/28) did not respond to chemotherapy regardless of the number of cycles given, (x2 = 0.491 (df–1), p = 0.483). Eventually, these unresponsive tumors will regrow or seed. Thus, a cutoff point should be established beyond which keeping the child on chemotherapy is no longer justifiable or curative. Similar recommendation is given by Zhao J, et al.23 who concluded that pre-enucleation chemotherapy in advanced Group E eyes increased the risk of metastatic death. We recommend a trial of chemotherapy to establish sensitivity of the tumor to chemotherapy. Chemo-resistant tumors and tumors extending extraocularly are enucleated after 2-3 cycles. Children with chemosensitive tumors are followed meticulously up to the age of 7 years. A high index of suspicion is maintained for tumor regrowth and new tumor formation. In such cases, two further cycles of chemotherapy and adjuvant therapy should be instituted. A maximum limit of 12 cycles of chemotherapy is advised.

Our study showed that primary chemotherapy and number of chemotherapy cycles did not affect the outcome for the globe. Another variable that was studied was the stage of disease at presentation. Only a small portion of the cohort, 9 of 28 eyes (32%) presented with less advance...
Outcome of children with retinoblastoma treated with primary chemotherapy


OUTCOME OF CHILDREN WITH RETINOBLASTOMA TREATED WITH PRIMARY CHEMOTHERAPY


CONFlict OF INTEREST
Authors declared no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE
NIL

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non Commercial 2.0 Generic License.