Efficacy of vincristine and carboplatin as chemo-reduction for advanced bilateral retinoblastoma, the Saudi experience

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Abstract

Purpose: To evaluate the efficacy of a 2-drug chemotherapy regimen without external-beam radiotherapy (EBRT) and/or without enucleation in bilateral retinoblastoma.

Methods: From 1996 to 2010, 79 patients were diagnosed with bilateral RB and were eligible for chemotherapy. Chemotherapy was administered prior to and/or following local therapy to the eye. All patients received 3 cycles of chemo-reduction with carboplatin and vincristine, additional cycles of the same or other chemotherapy, local therapy, EBRT and enucleation were determined according to re-evaluation by the ophthalmologist.

Results: Advanced disease was seen in 115 (79%) eyes (group IV and V: 96, Group D and E: 19) out of 146 affected eyes. Tumor response after chemotherapy was observed in 78 patients (98.7%); complete response in 25 (32.1%), partial response in 49 (62.8%) Four (5.1%) had progressive disease. A total of 50 (63.3%) patients required EBRT; 38 for persistent disease, 4 for progressive disease, 2 for new lesions, 2 for re-activation and 4 for disease control. Enucleation was required in 15 (19%). Secondary malignancies occurred in two patients who underwent EBRT; one osteogenic sarcoma and one rhabdomyosarcoma then later osteogenic sarcoma. The 10 year overall survival was 96.3% with a median follow-up time of 3.124 ± 0.536 years (95%CI: 2.074–4.174).

Conclusions: The 2-drug chemotherapy regimen combined with local therapy appears to be adequate therapy for low stage disease but not in patients with advanced disease. The occurrence of secondary cancers in this group of patients is worrisome further highlighting the deleterious effects of EBRT.

Keywords: Retinoblastoma, Chemo-reduction, Enucleation, External beam radiation therapy, Secondary malignancy

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Introduction

Retinoblastoma is the most common cancer of the eye in children, affecting 1 in 15,000 live births. If untreated, it is fatal, but with timely detection and multidisciplinary care using current technology and treatment protocols, more than 95% of patients can be successfully salvaged before the disease spreads outside the eye.1–3 The primary goal of therapy is to save the child’s life. However, retaining the affected eye, preserving vision, and good cosmetic results are also important. Classification of retinoblastoma is important to determine appropriate therapy for...
the affected eye(s) of the child, and to predict treatment outcome. The Reese–Ellsworth (R–E) classification was devised to predict the outcome of eyes treated with external beam radiotherapy (EBRT). The long-term complications of radiation for children with retinoblastoma constitutional mutations include a high lifelong risk of secondary non-retinoblastoma malignancies with poor survival rates. The International intraocular retinoblastoma classification (IIRC) was developed for prognosis of eyes with intraocular retinoblastoma treated with chemotherapy and/or focal therapy. Current treatments for intraocular retinoblastoma include enucleation, external beam radiation therapy, c Cryotherapy, laser photocoagulation, thermotherapy, brachytherapy with iodine 125 or ruthenium 106 plaques, subconjunctival chemotherapy, intra-arterial chemotherapy and systematic chemotherapy. Chemotherapy and focal therapy have replaced EBRT as the primary treatment worldwide. The goal of chemotherapy is to reduce the tumor volume for focal therapy (with c Cryotherapy, laser, thermotherapy, or plaque brachytherapy). For small, localized tumors (group A under the international classification system), focal consolidative therapy alone is effective with one study demonstrating 86% of tumors having lasting regression. Most chemotherapy protocols for larger tumors use 2- or 3-drug chemotherapy with Carboplatin, Etoposide, and Vincristine. Due to the fact that children with germ line retinoblastoma are at a higher risk of developing secondary tumors, we opted not to include etoposide in the chemo-reduction regimen for children with retinoblastoma as first line therapy. This review outlines our experience with a 2-drug regimen utilizing Vincristine and Carboplatin as chemo-reduction in children with retinoblastoma.

Patients and methods

This research study was reviewed and approved by the Institutional Review Board of King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, Office of the Research Affairs.

Treating facilities

King Khalid Eye Specialist Hospital (KKESH) is a Tertiary Center situated in Riyadh, Saudi Arabia. Most patients with retinoblastoma in the Kingdom are referred to KKESH where they are diagnosed, and their disease is classified and staged; therapy is then administered as deemed necessary by the ocul Oncologists. Children diagnosed with retinoblastomas that are eligible for systemic chemotherapy and/or external beam radiation therapy are referred to the King Faisal Specialist Hospital and Research Center (KFSH&RC) for further management. When patients are seen in KFSH&RC, pathology is confirmed and further work-up and staging are performed as deemed necessary.

Retinoblastoma team

The retinoblastoma team is comprised of the ocular oncologists, ophthalmologist and retinoblastoma coordinator in KKESH and the pediatric hematologist/oncologist, clinical nurse coordinator and radiation oncologist in KFSH&RC.

Patient population and study design

From 1996 to 2007 the Reese–Ellsworth (R–E) classification was used for children less than 14 years of age with retinoblastoma and from 2008 onward the International Intraocular Retinoblastoma Classification was adopted. Patients with Reese–Ellsworth (R–E) classification groups I, or International Intraocular Retinoblastoma Classification group A were not eligible for chemotherapy. Patients eligible for chemo-reduction were those with Reese–Ellsworth (D–E) classification, or International Intraocular Retinoblastoma Classification group B–E; patients with advanced disease received adjuvant chemotherapy. The chemo-reduction regimen consisted of Vincristine and Carboplatin given every 3 weeks for a total of 6 cycles. The number of cycles ranged from 2 to 9, depending on the examination of the patients and further recommendations from the ocul Oncologists. Patients were assessed following 2 cycles of chemo-reduction by the ocul Oncologists for further intervention mainly focal therapy and continuation of chemo-reduction. At the end of therapy, patients were reassessed; if there was complete response, no further therapy was delivered. If, however, the response was not satisfactory with progression, re-activation, or new lesions, then further therapeutic options including enucleation, external beam radiation therapy, and further chemotherapy were determined by the ocul Oncologists.

Results

From January 1996 to January 2010, a total of 79 patients were diagnosed with bilateral retinoblastoma and were eligible for chemo-reduction; they are the subject of this study. Median age at diagnosis was 0.9 years (Mean ± SEM: 1.27 ± 0.13, Min: 0.1-Max: 7.1), and 50.6% were male. Females presented at an earlier median age of 0.79 years (Mean ± SEM: 1.22 ± 0.20) compared to males at 0.94 years (Mean ± SEM: 1.32 ± 0.17), but this difference was not statistically significant (p = 0.505, Mann–Whitney U Test). Sixty-five patients (82.3%) presented with various signs and symptoms; 39 had leukocoria (median duration: 8 weeks), 8 had squint (median duration: 20 weeks), 8 had poor vision (median duration: 8 weeks), 3 had white reflex, 2 had orbital cellulitis and 2 had esotropia. Other symptoms such as red eye, abnormal red reflux, cat’s eye, eye lesion and no light perception were uncommonly seen; 1 each in our patient population. Advanced disease was seen in 115 (79%) eyes (Group IV–V: 96, Group D–E: 19) out of 146 affected eyes. Detailed information on staging is provided in Table I.

Tumor response after chemotherapy was observed in 78 patients (98.7%); complete response in 25 (32.1%), partial response in 49 (62.8%) and progressive disease in 4 (5.1%). A total of 50 patients (63.3%) required EBRT; 38 for persistent disease, 4 for progressive disease, 2 for new lesions, 2 for re-activation and 4 for disease control. Enucleation was required in 15 (19%). Secondary malignancies were seen in 2 patients who underwent EBORT; 1 patient developed osteogenic sarcoma and the other rhabdomyosarcoma then osteogenic sarcoma. Median time to develop secondary malignancy was 20.9 months from discontinuation of therapy. Sixty-eight of our patients (86.1%) were on follow-up after finishing treatment, 7 (8.9%) were lost to follow-up, 1 (1.3%) was referred to another hospital for continuation of treatment and...
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Several studies have established that chemotherapy is very effective in eliminating the need for EBRT/enucleation in R-E group I–III eyes, but the experience with eyes with group IV or V disease has been significantly less rewarding; the chemotherapy regimen commonly used consists of carboplatin, vincristine, and etoposide.\textsuperscript{14,16,17}

Secondary neoplasms in patients with retinoblastoma have been well recognized since the 1960’s. The majority occur in patients with bilateral disease who are exposed to EBRT after a prolonged latent period, but, they may also occur in patients who did not receive radiation therapy.\textsuperscript{10,18–22}

Etoposide is an anti-DNA topoisomerase II agent that has been widely used for the treatment of many types of cancers in children including retinoblastoma and has been associated with an increased risk of secondary leukemia specifically acute myeloid leukemia.\textsuperscript{23,24} Though the incidence of secondary acute myeloid leukemia is rare, there are several reports of its occurrence in retinoblastoma patients.\textsuperscript{24,25} Because of the potentially increased risk for secondary malignancies when using etoposide, in this study, we, like many others, opted for the 2-drug regimen consisting of Vincristine and Carboplatin at standard schedules and doses. Although this therapy was well tolerated with acceptable toxicity, many of the patients with advanced disease with the Reese–Ellsworth (R–E) classification group IV and V and patients with advanced disease using the International Intraocular Retinoblastoma Classification including group D and E required enucleation and/or external beam radiation therapy. This has been previously demonstrated in other studies utilizing chemo-reduction in an attempt to avoid enucleation or the need of EBRT. In a study by Friedman\textsuperscript{27}, 47 patients were treated with 6 cycles of vincristine, etoposide and carboplatin along with focal therapy in the majority of patients; for patients with less advanced disease, i.e. R–E group I–III, no enucleation or EBRT was necessary while in patients with advanced disease, i.e. R–E group IV and V, 33% of six eyes and 53% of 30 eyes, respectively, required EBRT and/or enucleation with the conclusion that more effective therapy is required for R–E group IV and V. Shields reported their results on 103 patients, 158 eyes, 75 (48%) eyes were R–E group V, 47% required EBRT while 53% underwent enucleation compared to lower stage disease patients in whom only 10% required EBRT and only 15% required enucleation. Murphee et al.\textsuperscript{28} also reported on 136 patients (172 eyes) who were treated and followed-up from 1990 to 1995; initially, the patients were treated with carboplatin and thermochemotherapy from 1990–1992, and after 1992 patients were treated with 3 monthly cycles of chemoreduction with vincristine, etoposide and carboplatin followed by sequential aggressive local therapy. Patients underwent eye examinations under anesthesia every 2–3 weeks. In patients with RE I–II thermochemotherapy was successful for larger tumors in the absence of vitreous or extensive subretinal seeding, 3 cycles of chemoreduction followed by sequential aggressive local therapy eradicates the residual viable tumor.

In this study of Saudi patients, the use of a 2-drug regimen did not seem to lessen the need for the use of EBRT or enucleation, corroborating the already published international data as discussed above. We have, consequently, modified our chemotherapy management for patients with the International classification group D and E to a 3-drug regimen containing vincristine, carboplatin and etoposide.

### Table I. The staging details of all patients.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Left Eye</th>
<th>Right Eye</th>
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<td>% (n)</td>
<td>% (n)</td>
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- **Reese-Ellsworth Classification**
  - Ia: 1.4 (1) 0 (0)
  - Ib: 1.4 (1) 1.4 (1)
  - Iic: 6.8 (5) 1.4 (1)
  - IIb: 2.7 (2) 2.8 (2)
  - IIIa: 4.1 (3) 8.3 (6)
  - IIIb: 1.4 (1) 5.6 (4)
  - IVa: 2.7 (2) 2.8 (2)
  - IVb: 5.4 (4) 2.8 (2)
  - Vaa: 10.8 (8) 8.3 (6)
  - Vab: 47.3 (35) 51.4 (37)

- **ICRB**
  - Group A: 2.7 (2) 0 (0)
  - Group B: 0 (0) 1.4 (1)
  - Group C: 0 (0) 1.4 (1)
  - Group D: 5.4 (4) 9.7 (7)
  - Group E: 8.1 (6) 2.8 (2)
  - Total: 93.7 (74) 91.1 (72)

Note: For 79 patients, information on 74 left and 72 right eyes was available. Staging was not done if either the eye was not affected or there was no eye present.

Further follow-up, and 3 (3.8%) expired due to progression of the secondary malignancies. The 12-year overall survival (Fig. 1) was 96.3% with a median follow-up time of 3.124 ± 0.536 years (95% CI: 2.074–4.174).

### Discussion

Management of a child with retinoblastoma requires a multidisciplinary approach including ophthalmologists, pediatric oncologists, radiation oncologists, and many others that play important roles in the cure of the disease.\textsuperscript{1–3} The current available therapeutic options are numerous, and the indications to use specific modality or combination of modalities vary according to the extent of the disease.\textsuperscript{6–8} Most patients with unilateral disease present with advanced intraocular disease and therefore usually undergo enucleation, which results in a cure rate >95%.\textsuperscript{9–11} On the other hand, children with bilateral disease at diagnosis usually require multimodality therapy (chemotherapy, local therapies)\textsuperscript{12–14}. Failure to control disease in children with bilateral disease may lead to external beam radiation EBRT and/or enucleation.\textsuperscript{15}

![Figure 1. Overall survival of all patients who underwent chemoreduction at KFSHRC.](image-url)
Conflict of interest

The authors declared that there is no conflict of interest.

References