

Scientific Session 6
Retinoblastoma 2

Shilpakalavedika Convention Center
Sunday, January 25, 2004
11:00 AM – 1:00 PM

Chair: John Hungerford
Co-chair: Vijay Anand Reddy
Moderator: Judith Kingston
Session Summary: Arun Singh

	Presenter	Title of Presentation	Time
1	Vijay Anand Reddy	Introduction to Anna Meadows	11:00 AM
2	Anna Meadows	Guest Lecture: Children's Oncology Group Retinoblastoma Protocols	11:02 AM
3	Gallie Brenda	Key Note Lecture: World Internet Survey of Classification of Retinoblastoma	11:20 AM
4	Ravi Yeddanapudi	A Decade of Chemoreduction Strategy in the Treatment of Retinoblastoma	11:35 AM
5	Mahesh Shanmugam	Possible Causes of Failure of Chemoreduction in Retinoblastoma - An Analysis	11:45 AM
6	Seema Anand	Lens Sparing Radiotherapy and Chemotherapy in the Treatment of Genetic Retinoblastoma	11:55 AM
7	Judith Kingston	Chemotherapy as the Sole Modality of Treatment for Intraocular Retinoblastoma	12:05 AM
8	Vasanth Thavaraj	Management of Retinoblastoma with Carboplatin, Etoposide, Vincristine and Cyclophosphamide	12:15 AM
9	Carol Shields	Chemoreduction for Retinoblastoma : Analysis of Tumor Control and Risks for Recurrence in 457 Tumors	12:25 AM
10	Victoria Cohen	The Success of Primary Chemotherapy for Bilateral Retinoblastoma with Reese Group 5 Disease	12:35 AM
11	Helen Chan	High-Dose Chemotherapy with Cyclosporine and Focal Therapy for International Classification Group C and D Retinoblastoma May Improve Ocular Salvage without Radiation	12:45 AM
12	Arun Singh	Session Summary	12:55 AM

GUEST LECTURE

CHILDREN'S ONCOLOGY GROUP RETINOBLASTOMA PROTOCOLS

Anna Meadows

The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine
Philadelphia, PA, USA

KEY NOTE ADDRESS

WORLD INTERNET SURVEY OF CLASSIFICATION OF RETINOBLASTOMA

Brenda Gallie

Princess Margaret Hospital, University of Toronto, Toronto, Canada

DECADE OF CHEMOREDUCTION STRATEGY IN THE TREATMENT OF RETINOBLASTOMA LESSONS AND FUTURE IMPLICATIONS

Ravindranth Yaddanapudi

Wayne State University, Detroit, MI, USA

It has been a little over 10 years since chemo-reduction strategy has been first utilized in the primary treatment of retinoblastoma. Experience has taught us that this strategy is highly successful, the individual tumors do regress in size; enucleation can be avoided in a significant number of cases especially with early stage disease and use of external beam radiation can be avoided. The clinical observations of sensitivity to chemotherapy have been supported by the lack of viable tumors at resection of enucleated eye that has received chemotherapy. The recent understanding of the role of RB gene in the regulation of apoptosis (Nature Reviews 2003) explains these observations. Experiences in RB knockout mice shows these mice do not develop retinoblastoma but show increased neuronal muscle cell loss. Transfection with caspase resistant RB retards the apoptosis noted in such cell systems suggesting that a normal function of RB is to block apoptosis. Thus loss of RB function, while it might predispose to development of retinoblastoma in the humans, might in fact be taken advantage of in designing effective chemotherapy. Future studies should aim at determining the role of the chemotherapy, not only in germline retinoblastoma but in unilateral sporadic retinoblastoma as well.

POSSIBLE CAUSES OF FAILURE OF CHEMOREDUCTION IN RETINOBLASTOMA – AN ANALYSIS

Mahesh Shanmugam, Vikas Khetan, Mallikarjuna Kandam, Amirtha Lakshmi Sundaram, Krishnakumar Subramanian, Neal Desai

Sankara Nethralaya, Chennai, India

PURPOSE: To study the role of clinical factors and Multi Drug Resistance (MDR) proteins in failure of chemoreduction in retinoblastoma. **METHODS:** Retrospective analysis of clinical features of 16 eyes enucleated following failure of chemoreduction; P glycoprotein and Lung Resistance protein (LRP) expression was studied in 8 of these 16 eyes. **RESULTS:** 10 eyes belonged to Reese Ellsworth (RE) stage 5, 4 to RE stage 4 and 1 eye to RE stage 3. LRP was positive in 6 and P glycoprotein in 2 of 8 eyes. **CONCLUSION:** Advanced RE staging appears to be a factor for failure of chemoreduction. MDR other than P glycoprotein may also play a role in failure of chemoreduction in retinoblastoma.

LENS SPARING RADIOTHERAPY AND CHEMOTHERAPY IN THE TREATMENT OF GENETIC RETINOBLASTOMA

Seema Anand, John Hungerford

Leeds General Infirmary, Leeds, UK

PURPOSE: To compare the outcome following lens sparing radiotherapy (LSRT) and chemotherapy (CT) in the management of genetic retinoblastomas. **METHODS:** All patients with genetic retinoblastoma (Reese-Ellsworth Groups I-III, age below 1 year at diagnosis) who received either LSRT or chemotherapy as primary treatment were reviewed retrospectively. This division was created as LSRT (1985-95) was replaced by chemotherapy (1995 onwards) as primary treatment in this group. Primary failure rates, salvage treatments required and outcome following salvage treatment were compared. **RESULTS:** Out of 110 eyes (84 patients), 61 were treated with radiotherapy (mean follow-up 92.55 months) and 49 with chemotherapy (mean follow-up 35.44 months). Primary failure rates were 47.55% and 71.43% respectively. Vitreous relapse rates of 1.63% (LSRT) and 10.2% (CT) were noted. An average of 2.14 salvage treatments per eye were needed following failure of radiotherapy as compared with 2.94 following chemotherapy. Overall success following salvage was comparable (96.4% LSRT, 93.87% CT) except in Reese-Ellsworth Group I tumors (100%LSRT, 84.6%CT). **CONCLUSION:** In spite of a shorter follow up, the primary failure rate was significantly higher with chemotherapy as compared to radiotherapy. There was a higher vitreous relapse rate and a higher number of salvage treatments needed per failed eye with chemotherapy.

CHEMOTHERAPY AS THE SOLE MODALITY OF TREATMENT FOR INTRAOCULAR RETINOBLASTOMA

Judith Kingston, John Hungerford

St Bartholomews Hospital, London, UK

During a 10-year period 1993-2002, 99 eyes with retinoblastoma were treated with chemotherapy as the sole primary treatment to determine which tumors could be treated by chemotherapy alone and which require additional focal therapy. Eighty-four of the eyes were in bilaterally affected individuals and 15 eyes were in unilaterally affected children. Treatment consisted of 6-8 courses of chemotherapy with Vincristine, Etoposide and Carboplatin. Twenty-one eyes (21%) required no further treatment. The Reese-Ellsworth grouping of the eyes which were successfully treated by chemotherapy alone, were group 1 in 5, group 2 in 12 and group 4 in 4. Of the 78 eyes that failed treatment with primary chemotherapy alone, 16 (20%) had new tumors only and most of these were amenable to cryotherapy. Of the eyes that developed local recurrences, 26(33%) required external beam radiotherapy. Less than 20% of eyes that failed chemotherapy subsequently required enucleation. This study shows that selected cases of retinoblastoma (21% of eyes in this series) can be treated by chemotherapy alone thus obviating the need for focal therapies, which have the potential to damage vision.

MANAGEMENT OF RETINOBLASTOMA WITH CARBOPLATIN, ETOPOSIDE, VINCRISTINE AND CYCLOPHOSPHAMIDE

Vasantha Thavaraj, Avinash, B Mohanty, S Nizamuddin, S Ghose, S Arya

All India Institute of Medical Sciences, New Delhi, India

PURPOSE: To evaluate carboplatin, etoposide, vincristine and cyclophosphamide in the management of retinoblastoma. **METHODS:** Hundred cases of retinoblastoma attending the Pediatric Oncology Clinic at the AIIMS from 1st Jan 1996 to

31st Dec 2002 were diagnosed by histopathological examination of the enucleated eyes. They were investigated for the extent of disease. They were given 12 cycles at 4 weekly intervals of cyclophosphamide, vincristine, carboplatin and etoposide. **RESULTS:** Hundred cases were enrolled for this chemotherapy protocol. The mean age at presentation was 24.0 months \pm 28.46 SD. There were 64 boys and 36 girls. There were 38 unilateral retinoblastoma (21 right eye and 17 left eye) and 62 bilateral retinoblastoma. According to St. Jude's Classification, there was only one case in stage I, 74 cases in stage II (73.5%); 21 cases in stage III (22.2%), and 4 cases in stage III (4.3%). Seventy-two cases underwent enucleation, 6 cases (6.9%) underwent exenteration and 21 cases were subjected to primary chemoreduction. Seventy-two (72.4%) cases are under follow up. Out of the 72 cases (18 cases are ongoing chemotherapy, 54 cases were on combined therapy) have been evaluated for survival status. The median follow up is 25 months (range 1 month – 75 months). The overall survival is 73.8%, the disease free survival is 75.6% at 5 years. **CONCLUSION:** The survival was affected by tumor cell infiltration of the optic nerve transection and by the stage of the disease.

CHEMOREDUCTION FOR RETINOBLASTOMA: ANALYSIS OF TUMOR CONTROL AND RISKS FOR RECURRENCE IN 457 TUMORS

Carol Shields, Arman Mashayekhi, Jacqueline Cater, Abdallah Shelil, Anna Meadows, Jerry Shields

Wills Eye Hospital Philadelphia, PA, USA

PURPOSE: To evaluate individual tumor control following chemoreduction for retinoblastoma. **METHODS:** A prospective nonrandomized study was performed on 125 patients managed with six cycles of chemoreduction (vincristine, etoposide, and carboplatin) alone (group A) or chemoreduction combined with focal consolidation using thermotherapy (group B), cryotherapy (group C), or both thermotherapy and cryotherapy (group D) to each retinoblastoma. **RESULTS:** Of 457 retinoblastomas, 63 were in group A, 256 in group B, 127 in group C, and 11 in group D. Macular tumor location was noted in 53% of group A, 42% of group B, 2% of group C, and 9% of group D. The mean tumor thickness at initial examination was 7 mm for group A, 4 mm for group B, 2 mm for group C, and 3 mm for group D. Using Kaplan-Meier analysis, recurrence of the individual retinoblastoma at 6 years was found in 45% of group A and 18% of combined groups B, C, and D. Factors predictive of tumor recurrence by multivariate analysis included Caucasian race, macular tumor location, large tumor size, and lack of tumor consolidation (Group A). **CONCLUSION:** Chemoreduction alone or with focal consolidation can be effective approaches for management of retinoblastoma, but focal consolidation provides best long-term tumor control.

THE SUCCESS OF PRIMARY CHEMOTHERAPY FOR BILATERAL RETINOBLASTOMA WITH REESE GROUP 5 DISEASE

Victoria Cohen, Judith Kingston, John Hungerford

St Bartholomews Hospital, London, UK

PURPOSE: To assess the need for enucleation following first line chemotherapy for bilateral retinoblastoma (RB), when one or both eyes have Reese group 5 involvement. **METHODS:** The RB database was used to select all children treated with primary chemotherapy. Only children with bilateral disease, having Reese group 5 tumors in one or both eyes and more than one year's follow-up was included in the study. The need for enucleation, time from diagnosis to enucleation and the number of globe salvage treatments were recorded. **RESULTS:** Since 1995, chemotherapy has been used as the primary treatment for bilateral RB in our unit. 15 children with bilateral RB had Reese group 5 tumors. A total of 18 eyes had group 5

disease, of which 7 (39%) required enucleation for resistant RB. 9(82%) of the remaining 11 eyes received salvage treatment to avoid enucleation, 50% requiring more than one. The median time from diagnosis to enucleation was 9 months (range 4 - 25 months). **CONCLUSION:** Primary chemotherapy success rates are poor in Reese group 5 RB and salvage treatments are frequently required. When one eye is more severely affected than the other, early enucleation may be preferable to multiple attempts to save a blind eye with metastatic potential.

HIGH-DOSE CHEMOTHERAPY WITH CYCLOSPORINE AND FOCAL CRYO/LASER THERAPY FOR INTERNATIONAL CLASSIFICATION GROUP C AND D INTRAOCULAR RETINOBLASTOMA MAY IMPROVE OCULAR SALVAGE WITHOUT RADIATION

Helen Chan, Elise Heon, Andrew Budning, Brenda Gallie

The Hospital for Sick Children, University of Toronto, Toronto, Canada

PURPOSE: We previously reported that standard-dose chemotherapy with cyclosporine (which may inhibit multidrug resistance), avoided radiation or enucleation for eyes with Groups C (77%) and D (23%) retinoblastoma. We increased the doses of chemotherapy on this protocol to improve results for high-risk eyes. **METHODS:** Since 2000, we treated 18 eyes (13 Group D, 5 Group C) in 12 newly diagnosed children with cyclosporine-modulated high-dose carboplatin and etoposide, standard-dose vincristine, and focal therapy. Radiation or enucleation for recurrent disease was considered treatment failure. **RESULTS:** Eye event-free rates (median follow-up 2 years) were 60% for Group D (8/13) and Group C (3/5) eyes. Five Group D eyes (4 patients) failed; 3 patients had one eye enucleated and retained the other eye, and 1 had radiation to one eye and enucleation of the other eye. Two Group C eyes (2 patients) failed; both had one eye enucleated and retained the other eye. No child lost both eyes. **CONCLUSION:** Although follow-up is short, preliminary outcomes indicate that most children can avoid radiation (100% of Group C and 85% of Group D eyes) while retaining vision. Higher dosages of carboplatin and etoposide with cyclosporine appear to improve success rates for Group D eyes.

SESSION SUMMARY

Arun Singh

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