NEOPLASIA
www.neoplasia.com

Volume 20 Number 8 August 2018 pp. 757–763 757

Current Treatment of Bilateral Retinoblastoma: The Impact of Intraarterial and Intravitreous Chemotherapy

Jasmine H. Francis[*,†], Nelli Roosipu[‡], Ariana M. Levin[†], Scott E. Brodie[§], Ira J. Dunkel[*,†], Y. Pierre Gobin[†] and David H. Abramson[*,†]

[*]Memorial Sloan Kettering Cancer Center, New York, NY 10065; [†]Weill Cornell Medical College, New York, NY 10065; [‡]Tartu University Clinic, Tartu 50406, Estonia; [§]NYU-Langone Medical Center, New York, NY 10016

Abstract

PURPOSE: To evaluate the management and outcomes of naïve bilateral retinoblastoma treated at a single-center over a 5-year period during the era of ophthalmic artery chemosurgery (OAC) and intravitreous chemotherapy. *METHODS:* Retrospective cohort study of 46 patients (92 eyes) with naïve bilateral retinoblastoma treated at Memorial Sloan Kettering Cancer Center between January 2012 and February 2017. Indirect ophthalmoscopy, fundus photography, ultrasonography, and ultrasonic biomicroscopy were used to evaluate clinical response. Patient, ocular, ocular progression-free, ocular recurrent event–free, and second ocular survivals were assessed by Kaplan-Meier estimates. Retinal toxicity was evaluated by electroretinography. Snellen visual acuity and complete blood count metrics were recorded. *RESULTS:* Sixty-four eyes (70%) in 41 patients (89%) received ophthalmic artery chemosurgery as part of their treatment. Twenty-six patients (56%) received tandem OAC (bilateral simultaneous infusions). Seven eyes were primarily enucleated. No eye receiving initial OAC was enucleated. There was a single secondary enucleation in an eye initially treated with focal therapy with anterior chamber recurrence. The 3-year Kaplan-Meier estimates for overall ocular, secondary ocular (survival after treatment for recurrence), progression-free, and recurrent event–free survival were 91.3% [95% confidence interval (CI) 83.4-95.5], 98.7% (95% CI 91.3-99.8), 91.5% (95% CI 83.0-95.8), and 78.9% (95% CI 68.2-86.3), respectively. Overall and secondary ocular survivals were 100% for International Classification of Retinoblastoma (ICRB) groups A-C. Overall ocular survival was 91.5% (95% CI 70-97.8) for ICRB group D and 71.4% (95% CI 47.1-79.4) for group E. Secondary ocular survival was 95.4% (95% CI 71.8-99.3) for ICRB group D and 100% for group E. There were no treatment-related deaths, three patients developed trilateral retinoblastoma (one died), and one patient (who did not receive OAC) developed metastatic disease and is in remission at 32-month follow-up. *CONCLUSION:* The majority (89%) of bilateral retinoblastoma patients in the current era and at this center were treated with OAC. This has resulted in saving a historic number of eyes. A quarter of eyes developed recurrent disease (defined as recurrent disease requiring any treatment including focal), the majority of which occurred in the first year after treatment, and all but one was saved. There has been no compromise in patient survival.

Neoplasia (2018) 20, 757–763

Introduction

Retinoblastoma involving both eyes occurs in a third of patients, is accompanied by a germline *RB1* mutation, and is uniquely devastating. Patients are at risk for potentially losing both eyes and losing vision in both eyes, and unlike the majority of unilateral patients, they are at increased risk for second primary malignancies (SPMs) and having children with the disease. These factors have influenced how the management of bilateral retinoblastoma has evolved over decades and continues to change at present (Table 1) [1–10].

As treatment modalities for retinoblastoma advance over the decades, centers have reported specifically on how patients with

Abbreviations: SPMs, second primary malignancies; EBR, external beam radiation; OAC, ophthalmic artery chemosurgery; ERG, electroretinogram; PFS, progression-free survival (an event included any treatment with enucleation, external beam radiation and OAC following completion of initial treatment and was calculated from the initial treatment date); ReFS, recurrent event–free survival (an event was defined as recurrence if receiving any treatment, including focal. and calculated from the end date of the initial treatment to date of recurrence diagnosis).

Address all correspondence to: Jasmine H. Francis, MD FACS, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065.
E-mail: francij1@mskcc.org

Received 6 April 2018; Revised 29 May 2018; Accepted 31 May 2018

1476-5586/18
https://doi.org/10.1016/j.neo.2018.05.007

bilateral retinoblastoma fair with contemporary managements. The evolution of these treatments and the outcomes for retinoblastoma patients are summarized in Table 1. Historically, bilateral retinoblastoma was treated with bilateral enucleation, rendering the patient blind and severely impacting quality of life. In 1936, in an effort to improve vision and quality of life, Reese et al. introduced the approach of enucleation of the more advanced eye and treatment of the fellow eye with external beam radiation (EBR) [1]. As radiation techniques evolved, some eyes were then treated with simultaneous bilateral radiation [4-11]. Despite no difference in metastatic deaths between double enucleation and bilateral radiation [4], it was later recognized that radiation increased the risk of SPMs (and therefore mortality) in this genetically primed group of patients [12].

Some groups combined systemic chemotherapy with radiation as globe-conserving treatment for the only remaining but advanced eye with the hope of being able to deliver less radiation [5]. Subsequently, systemic chemotherapy alone was used to treat the remaining eye or both eyes in appropriate cases [6,7]. However, chemoreduction was observed to be less efficacious than primary EBR [8]. Besides focal treatments, failed cases often received secondary EBR: an approach that potentially increases the SPM risk from combination chemotherapy and radiation. Furthermore, the toxic effects of systemic chemotherapy (myelosuppression, ototoxicity, and secondary malignancies) made it a less attractive treatment option. Ototoxicity would be particularly devastating in a child afflicted with bilateral disease and impaired vision.

Since May 2006, our center has been treating retinoblastoma patients with ophthalmic artery chemosurgery (OAC), which involves selective catheterization of the ophthalmic artery and focal delivery of chemotherapy. We initially treated single eyes with advanced disease but quickly advanced to simultaneous bilateral OAC (tandem therapy) [13]. Due to the impressive ocular salvage, improved toxicity profile over systemic chemotherapy, and no increased risk for metastatic deaths [14], we have abandoned EBR and multiagent systemic chemotherapy in the treatment of intraocular retinoblastoma (for unilateral or bilateral disease). OAC has become our standard of care for both unilateral and bilateral patients. This study evaluates how the OAC era, along with the introduction of intravitreous chemotherapy in 2012, has influenced the care and outcome of naïve bilateral retinoblastoma patients treated at the Memorial Sloan Kettering Cancer Center (MSKCC).

Methods

This MSKCC Institutional Review Board–approved retrospective study included all bilateral retinoblastoma patients who presented consecutively to MSKCC between January 2012 and July 2016 and had not received any prior treatment. Patients not treated with OAC were included. Included patients required at least 3 months of follow-up by end of study period. Data collection ended February 28 2017. No child was lost to follow up. Informed consent for treatment was obtained for each patient from his/her guardian, caregiver, or parent. The study was Health Insurance Portability and Accountability Act compliant. Research adhered to the tenets of the Declaration of Helsinki.

Ophthalmic artery chemosurgery was given to 64 eyes in a manner previously described [15]. The drug dosages were selected based on the following age-dependent guidelines {Francis:2015wn}: age 3-6 months: melphalan 2.5-3 mg, topotecan 0.3 mg, carboplatin 30 mg; 6-12 months: melphalan 3 mg, topotecan 0.5 mg, carboplatin 30 mg; 1-3 years: melphalan 4 mg, topotecan 1 mg, carboplatin 40 mg; >3 years: melphalan 5 mg, topotecan 1 mg, carboplatin 40 mg; and number of drugs was titrated to the extent of tumor/advancement of disease. The final drug dose and number of drugs depended on additional factors including route of drug administration (via ophthalmic artery versus balloon technique versus middle meningeal), perfusion and distribution of blood vessel, prior response to treatment, and the aim of maintaining cumulative melphalan dose less than 0.4 mg/kg between both eyes (to prevent myelosuppression). Monthly examinations assessed tumor response and the need for additional OAC infusions based on tumor regression.

Radiation exposure potentially increases the risk of SPMs, particularly in genetically primed bilateral retinoblastoma patients. As such, our group takes extra precautions to significantly reduce radiation exposure during the OAC procedure (by using short fluoroscopy times and minimal use of subtraction angiography). As such, our group's average radiation exposure is 35 to 194 times lower than published doses from other groups [16].

Bridge patients were those less than 3 months of age who received systemic chemotherapy (single-agent carboplatin 18.7 mg/kg in the majority of cases, although vincristine and etoposide were also used; details below) with the intention of receiving subsequent OAC once 3 months of age and body weight of 6 kg were reached. Ten eyes did not require subsequent OAC and were termed partial bridge. The intravitreous (melphalan 30 μg and topotecan 20 μg) and periocular (topotecan 1 mg) injections were performed as previously described [17] and were given to 15 eyes. Periocular topotecan was given to eyes with diffuse seeding that had demonstrated inadequate response to prior intravitreous melphalan alone. Injections were given at a weekly to monthly interval, predominantly based on the patients' availability (with a trend towards monthly injections if feasible). Eyes with

Table 1. Published, Historical Data for Naïve Bilateral Retinoblastoma

Author	Year	Subjects	No. Pts.	No. Eyes	Treatment	Patient Survival	Overall OS	Primary Enuc	Secondary OS
Reese	1949	bl	53	106	enuc advanced, EBR less advanced	41/53 (77%)	43/106 (41%)	53/106 (50%)	40/53 (75%)
Abramson	1979	bl	24	48	bl enuc	19/24 (80%)	0%	48/48 (100%)	0%
Gagnon	1980	bl	25	50	enuc advanced, EBR if less advanced	67.6% at 5 yrs	22/50 (44%)	22/50 (50%)	22/28 (79%)
Abramson	1981	RE IV or V	32	64	bilateral EBR	28/32 (88%)	19/64 (30%)	NR	19/64 (30%)
Abramson	1981	RE I to III	37	74	bilateral EBR	30/32 (94%)	63/74 (85%)	NR	63/74 (85%)
Haye	1987	bl rb eye RE V)	33	66	systemic chemo, EBR	15/23 (63%)	NR	18/66 (27%)	7/21 (33%)
Kingston	1996	RE V	14	28	systemic chemo, EBR	12/14 (86%)	17/28 (61%)	4/28 (14%)	17/24 (71%)
Gallie	1996	bl	31	62	chemoreduction	30/31 (97%)	38/62 (61%)	22/62 (35%)	38/40 (95%)
Lee	2003	bl, one eye enuc	107	107	systemic chemo, radiation, focal	100/108 (93%)	72/214 (34%)	107/214 (50%)	72/107 (67%)
Sohajda	2006	bl, one eye enuc	13	26	systemic chemo, brachy	12/13 (93%)	12/26 (46%)	13/26 (50%)	12/13 (93%)
Berry	2013	bl, only IC D	49	62	systemic chemo, IMRT, brachy, focal	NR	NA	NA	45/55 (82%)
Francis	2018	bl	46	92	majority OAC	41/42 (98%)	84/92 (91%)	7/92 (7.6%)	83/84 (99%)

No., number; *Pts.*, patients; *Enuc*, enucleation; *bl*, bilateral; *brachy*, brachytherapy; *IMRT*, intense modulated radiation therapy; *yrs*, years; *mos*, months; *NR*, not recorded; *NA*, insufficient data on fellow eyes.