Irradiation Toxic Effects During Intra-arterial Chemotherapy for Retinoblastoma

Should We Be Concerned?

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Objective: To evaluate irradiation toxic effects from fluoroscopy during intra-arterial chemotherapy for retinoblastoma.

Design: Prospective trial.

Participants: Eight patients treated with intra-arterial chemotherapy.

Main Outcome Measures: Irradiation toxic effects in vital organs.

Results: The mean patient age was 29 months (range, 10-74 months) and 63% were male. The mean irradiation dose to the skin of the affected eye was 0.19173 Gy, to the contralateral eye was 0.03533 Gy, to the chest wall was 0.00296 Gy, and to the abdominal wall was 0.00104 Gy. The estimated irradiation dose to the lens in the treatment eye was 0.16 Gy, which, in accumulated doses, could be cataractogenic. The estimated irradiation dose from a single fluoroscopy session to other organs, including the brain (0.05560 Gy), thyroid (0.00192 Gy), bone marrow (0.00059 Gy), and gonads (0.00015 Gy), was far lower than the minimal toxic level.

Conclusions: Careful use of fluoroscopy during intra-arterial chemotherapy with limited irradiation exposure is advised. Accumulated irradiation toxic effects following multiple sessions of intra-arterial chemotherapy could be cataractogenic and possibly carcinogenic, especially in irradiation-sensitive patients with retinoblastoma.


Intra-arterial chemotherapy is a promising new technique for retinoblastoma management with selective delivery of chemotherapy through the catheterized ophthalmic artery to the eye with minimal systemic chemotherapy adverse effects. Abramson and coworkers1 evaluated 9 patients with advanced or recurrent retinoblastoma treated with intra-arterial chemotherapy and demonstrated remarkable short-term tumor control. Shields and associates2 confirmed the efficacy of intra-arterial chemotherapy for retinoblastoma in which other treatment methods failed, and they further emphasized the difficulty and necessary precision in catheterization of the obliquely exiting ophthalmic artery from the internal carotid artery in young children. This requires use of cerebral fluoroscopy, which involves short, interrupted exposures to irradiation.

As with every new technique, there are concerns for short-term and long-term adverse effects. Local short-term adverse effects of intra-arterial chemotherapy include eyelid edema and ptosis, suprabrow cutaneous erythema and swelling, conjunctival chemosis, temporary restricted ocular motility, retinal detachment, and ophthalmic artery obstruction. Systemic short-term adverse effects of intra-arterial chemotherapy include fever, nausea, and mild transient cytopenia.1 Long-term adverse effects are yet to be described because this technique has been available in the United States for less than 5 years.

Intra-arterial chemotherapy for retinoblastoma is a neuroinvasive procedure and there are serious risks of stroke, cerebral hemorrhage or infection, systemic arterial fibrosis, and other severe neurological problems. Yamane and associates3 reported extensive experience with 187 children with retinoblastoma who received 563 cannulations (mean, 3 cannulations per patient), with a technical success rate of 98% and no reported cannulation-related complications, such as hemorrhage, stroke, or death.

During the procedure of intra-arterial chemotherapy, the catheter is placed transcatheterously into the femoral artery and ad-
Patients with retinoblastoma treated with intra-arterial chemotherapy at Wills Eye Institute in conjunction with the Jefferson Hospital for Neurosurgery at Thomas Jefferson University, Philadelphia, Pennsylvania, between January 2009 and September 2009 were included in the study. Institutional review board approval for intra-arterial chemotherapy was obtained. The clinical data at initial examination included age, race (African American, Hispanic, Asian, white), sex (female, male), affected eye (right, left), family history, laterality, height, and weight. The tumor data included tumor classification (International Classification of Retinoblastoma), tumor basal dimension (in millimeters), tumor thickness (millimeters by ultrasonography), extent of subretinal seeds, and extent of vitreous seeds. During the intra-arterial chemotherapy procedure, microStar radiation dosimeters (Landauer, Glenwood, Illinois) were used to measure the cumulative irradiation exposure at the skin level. For each patient, the dosimeters were placed at the lateral canthus of each eye, thorax (placed on the midsternal line at the level of the nipples), and abdomen (over the umbilicus). The dosimeter values were calculated per each catheterization and the individual organ irradiation exposure was estimated based on previous reports of organ toxic reaction.6-10

There were 8 children with retinoblastoma treated with 11 intra-arterial chemotherapy sessions included in the analysis. The mean age was 29 months (median, 23 months; range, 10-74 months) and 5 (63%) were male and 3 (37%) were female (Table 1). There were 7 white children (88%) and 1 Asian child (12%). All cases had no family history of retinoblastoma and 7 (88%) had unilateral disease and 1 (12%) had bilateral disease. Genetic analysis was performed on 7 of the 8 patients and was positive in only the child with bilateral retinoblastoma. Only 1 eye was treated in each case (Table 1). The intra-arterial chemotherapy was used as the primary treatment in 6 patients and was used to treat recurrence after previous treatments in 2 patients. The 2 patients in whom intra-arterial chemotherapy was used as a salvage treatment had previously received systemic chemotherapy and local cryotherapy. The clinical features of the tumors are listed in Table 1. The stage of tumor according to International Classification of Retinoblastoma was group A (n=0), group B (n=0), group C (n=1; 12%), group D (n=0), group E (n=5; 64%), and recurrent tumor (n=2; 24%). The mean tumor basal dimension was 18 mm (median, 18 mm; range, 10-22 mm) and the mean thickness was 8 mm (median, 8 mm; range, 3-13 mm). Subretinal seeds were seen in 5 patients (63%) (focal seeds in 1 [13%] and diffuse seeds in 4 [50%]). Vitreous seeds were seen in 7 patients (88%) (focal seeds in 1 [12%] and diffuse seeds in 6 [76%]).

The mean height of the patients was 88 cm (median, 87 cm; range, 74-116 cm) and the mean weight was 13 kg (median, 12 kg; range, 8-22 kg). The irradiation exposure to each anatomic site is listed in Table 2. The maximum irradiation exposure was to the treatment eye, at a mean of 0.19173 Gy (median, 0.16840 Gy; range, 0.06235-0.46611 Gy). The irradiation exposure to the contralateral eye was approximately 5 times less compared...
with the treatment eye, averaging to 0.03533 Gy (median, 0.02599 Gy; range, 0.00578-0.10292 Gy). This irradiation exposure decreased progressively according to distance from the treatment eye and was approximately 65 times less at the level of the thorax (mean, 0.00296 Gy; median, 0.000245 Gy; range, 0.000114-0.00790 Gy). The irradiation exposure decreased further at the level of the umbilicus, amounting to approximately 184 times less compared with the treatment eye (mean, 0.000104 Gy; median, 0.000077 Gy; range, 0.00033-0.00435 Gy).

Using previous studies, the correlation between skin entrance dose and organ toxic reaction can be calculated.\(^6\)\(^-\)\(^10\) (The percentage of organ irradiation dose to the skin dose was calculated from the reported values in the previous studies.) Though this is only an approximation, it provides a reasonable estimate of irradiation exposure to internal organs. The irradiation dose to the lens was approximately 87% of the ipsilateral lateral canthus skin dose, dose to the brain was 29% of the lateral canthus skin dose, dose to the thyroid gland was 65% of the midsternal chest wall skin dose, dose to the bone marrow was 20%, and dose to the gonads was 14% of the abdominal umbilicus skin irradiation dose.\(^6\)\(^-\)\(^10\)

Using these organ dose approximations, the internal organ exposure was calculated and is represented in Table 3. The average irradiation dose to the lens in the treatment eye was 0.16681 Gy and to the contralateral eye was 0.03074 Gy. The average dose to the brain was 0.00556 Gy, to the thyroid gland was 0.00192 Gy, to bone marrow was 0.00059 Gy, and to the gonads was 0.00015 Gy.

The mean follow-up time after intra-arterial chemotherapy was 4 months (range, 1-6 months). During the follow-up, no lens changes were witnessed in any of the patients. Only 1 patient underwent enucleation during the follow-up period and pathology results did not show any cataractous changes.

**Table 2. Cutaneous Irradiation Exposure During 11 Sessions of Intra-arterial Chemotherapy**

<table>
<thead>
<tr>
<th>Site of Exposure as Measured by microStar Radiation Dosimeters(^a)</th>
<th>Irradiation Level, Gy (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment eye</td>
<td>0.19173</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.16840 (0.06235-0.46611)</td>
</tr>
<tr>
<td>Contralateral eye</td>
<td>0.03533</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.02599 (0.00578-0.10292)</td>
</tr>
<tr>
<td>Thorax</td>
<td>0.00296</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.00245 (0.000114-0.00790)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.00104</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.00077 (0.00033-0.00435)</td>
</tr>
</tbody>
</table>

\(^a\) Manufactured by Landauer, Glenwood, Illinois.

**Table 3. Estimated Organ Irradiation Dose During 11 Sessions of Intra-arterial Chemotherapy\(^a\)**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Approximate Organ Dose(^a)(^6)(^-)(^10)</th>
<th>Estimated Irradiation Dose, Gy (N=11)</th>
<th>Established Irradiation Dose Toxic Level Harmful to the Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens</td>
<td>0.5 Gy(^11)</td>
<td>Treatment eye</td>
<td>0.16681</td>
</tr>
<tr>
<td></td>
<td>0.5 Gy(^11)</td>
<td>Median (range)</td>
<td>0.14651 (0.05424-0.40552)</td>
</tr>
<tr>
<td></td>
<td>1.1 Gy(^13)</td>
<td>Contralateral eye</td>
<td>0.003074</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Mean</td>
<td>0.00556</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Median (range)</td>
<td>0.04884 (0.01808-0.13517)</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Thyroid gland</td>
<td>0.00192</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Mean</td>
<td>0.00059</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Median (range)</td>
<td>0.00049 (0.00023-0.00158)</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Bone marrow</td>
<td>0.00015</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Mean</td>
<td>0.000011 (0.000005-0.00061)</td>
</tr>
<tr>
<td></td>
<td>2 Gy(^14)</td>
<td>Median (range)</td>
<td>0.000011 (0.000005-0.00061)</td>
</tr>
</tbody>
</table>

\(^a\) Superscripts represent the reference number from which the toxic level for the organ was obtained.

There are numerous terms to describe irradiation dose to human tissue, including background equivalent radiation time (BERT), critical organ dose (COD), dose area product (DAP), diagnostic acceptable reference level (DARling), effective dose (ED), fetal absorbed dose (FAD), total imparted energy (TIE), and surface absorbed dose (SAD).\(^13\) Surface absorbed dose, which is also known as entrance skin dose, is the amount of energy imparted per gram of tissue at the entrance surface.\(^10\) The European Union has identified surface absorbed dose as the diagnostic reference parameter in optimizing irradiation dose\(^17\) and was therefore used as the measurement for irradiation dose in this study.

Irradiation imaging of pediatric patients is unique in that the tissues are more radiosensitive in this population and there is a longer lifetime for irradiation-related cancer.\(^19\) Data from atomic bomb survivors have been pivotal in the understanding of irradiation carcinogenesis. Individuals exposed 50 years ago to doses comparable with those associated with helical computed tomography today show a small but statistically significant increased incidence of cancer. Using this information, a child undergoing an abdominal helical computed tomographic scan has a lifetime risk of fatal cancer approximately 1 in 1000.\(^19\) Brenner and coworkers\(^20\) reported that the estimated lifetime cancer mortality risks attributable to the irradiation exposure from computed tomography in a 1-year-old are 0.18% (abdominal) and 0.07% (head). Keeping in mind the potential toxic effects of pediatric irradiation exposure, the principle of “As Low As Reasonably Achievable” (ALARA) should be exercised to minimize irradiation dose.

The crystalline lens is one of the most radiosensitive tissues in the body.\(^21\) Recent studies indicate that the threshold for cataract development is less than was previously estimated and is approximately 0.5 Gy.\(^11\) The re-
view article by Ainsbury and coworkers\textsuperscript{11} summarized the results of recent mechanistic and human studies (including clinical exposure, atomic bomb survivors, Chernobyl, occupational exposure, and space flight exposure). They postulated that previous higher irradiation threshold values were obtained because of shorter follow-up and deficient identification of all cases. In our study, the average irradiation exposure to the lens during a single intra-arterial chemotherapy procedure was 0.16 Gy to the treatment eye and 0.03 Gy to the contralateral eye. The maximum irradiation dose to the lens in our study was 0.4 Gy, which approaches the cataractogenic dose. Also to be considered is the cumulative toxic effects from repeated intra-arterial chemotherapy doses. Most children require 3 to 4 intra-arterial chemotherapy sessions for complete tumor control and this would increase the cumulative dose to the lens, increasing the probability of cataract development in the treatment eye and possibly the contralateral eye. In most instances, irradiation-related cataract develops within 2 to 3 years (range, 0.3–35 years), so the exact risk will be evident in the near future.\textsuperscript{22}

The average brain irradiation dose in our study was 0.05 Gy with a maximum of 0.13 Gy. Studies on stereotactic irradiation have shown that limited brain irradiation at a dose of 50 to 60 Gy is safe with minimal to no discernable effect on memory and cognition.\textsuperscript{12} The approximate dose to the brain during intra-arterial chemotherapy is well below the toxic level and therefore likely safe.

The thyroid gland in children has one of the highest risk coefficients of any organ and is the only solid organ tissue with convincing evidence for risk at about 1.1 Gy.\textsuperscript{13} The thyroid irradiation dose in our study was a mean of 0.002 Gy with a maximum level of 0.005 Gy, which is lower than the toxic dose to pediatric thyroid tissue. Ron and coworkers\textsuperscript{14} also suggested that spreading the dose over time (from a few days to > 1 year) may lower risk, possibly because of the opportunity for cellular repair mechanisms to operate. The average interval between intra-arterial procedures is 4 weeks and this could aid in minimizing organ irradiation toxic effects.

The bone marrow and gonads are other structures that have an increased sensitivity to irradiation, particularly in growing children.\textsuperscript{18} In our study, the average irradiation dose to bone marrow was 0.0006 Gy (maximum, 0.00158 Gy) and to the gonadal tissue was 0.0002 Gy (maximum, 0.00061 Gy). The irradiation level above which toxic effects appear for bone marrow is 2 Gy and for gonads is 2 Gy.\textsuperscript{13,14} The irradiation dose to these organs in this study was far lower than the level of toxic effects.

The increased sensitivity of retinoblastoma cells to irradiation has been demonstrated and well documented in cell culture studies.\textsuperscript{23,24} Marees and associates\textsuperscript{25} reported that the cumulative mortality from any second malignancy 50 years after retinoblastoma diagnosis was 17.3% for patients with hereditary disease. Hence, extra caution needs to be exercised in patients with retinoblastoma with hereditary mutation causing susceptibility to fatal second cancers. Also, the age of the patient prior to considering intra-arterial chemotherapy should be noted because the irradiation susceptibility is higher in patients younger than 1 year.

Because intra-arterial chemotherapy is a relatively new technique, the risks and adverse effects are still poorly understood. With better understanding of the irradiation damage during the procedure, the neurovascular interventionalists can modify the fluoroscopy time and dose to minimize toxic effects.

In summary, fluoroscopy for catheter guidance is essential for intra-arterial chemotherapy for retinoblastoma. However, concerns exist regarding irradiation toxic effects from fluoroscopy in children. In this analysis, we found that there was a measurable irradiation dose to the lens in the affected eye. The latent period to develop cataract can be very variable, and hence, long-term follow-up is advisable. For patients who have received treatments other than intra-arterial chemotherapy, the lens could be more susceptible to irradiation damage and increase their propensity to develop cataract. The irradiation dose to other organs was lower than the level of toxic effects. Nevertheless, reasonable caution is advised in the use of fluoroscopy during intra-arterial chemotherapy. Children with retinoblastoma are more susceptible to irradiation-related second cancers and could be more prone to malignancy with even low doses of irradiation. Long-term close monitoring of these children is mandatory for both ocular and systemic effects of irradiation and chemotherapy.

Correction

Errors in End Matter. In the Ophthalmic Molecular Genetics article titled “Evidence for Keratoconus Susceptibility Locus on Chromosome 14: A Genome-wide Linkage Screen Using Single-Nucleotide Polymorphism Markers” by Liskova et al, published in the September issue of the Archives (2010;128[9]:1191-1195), 2 sections of end matter were accidently omitted. There should have been an Author Contributions section that read “Drs Liskova and Hysi contributed equally to this work. Drs Liskova and Hysi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.” and an Additional Contributions section that read “Quincy Prescott, MSc (Institute of Ophthalmology, University College London), provided technical support for the project and Kerra Pearce (UCL Genomics) assisted with sample processing. We thank Alison J. Hardcastle (Institute of Ophthalmology, University College London) for valuable comments on the study design.”