

Use of intra-arterial chemotherapy for retinoblastoma: results of a survey

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Abstract

• **AIM:** To obtain baseline knowledge about the current use of intra-arterial chemotherapy (SSOAIC) in centers worldwide.

• **METHODS:** A survey including questions about the use of SSOAIC was emailed to retinoblastoma experts.

• **RESULTS:** Seventy-nine (response rate 69.9%) doctors from 63 centers in 35 countries responded. Thirty-one centers from 19 countries use SSOAIC. Twelve performed more than 50 procedures. Melphalan is the most commonly used drug but 15 centers use more than one drug. First line therapy for advanced unilateral disease is the most common use of SSOAIC (74.2%). Centers with larger experience (>50 applications) were less likely using melphalan alone ($P=0.06$) and significantly more likely using SSOAIC in more situations such as second line in preference to radiotherapy $P=0.05$. Nineteen (61.2%) stated that SSOAIC improved their results and 21 (77.8%) reported less toxicity compared to other treatments. Three centers reported that SSOAIC did not improve their results. There were regional variations in the use of SSOAIC which is used more frequently as secondary treatment in Europe compared to the USA and Japan. Ten centers identified cost is the major limiting factor for SSOAIC.

• **CONCLUSION:** SSOAIC is used in an increasing number of centers worldwide with regional variations. Centers with more experience in SSOAIC use it in more situations including other drugs than melphalan. The majority of the centers using this technique reported

improved results and few complications.

• **KEYWORDS:** retinoblastoma; intra-arterial chemotherapy; survey

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INTRODUCTION

Retinoblastoma is the most common pediatric intraocular malignancy, occurring in about 4-5 cases per million children from 0 to 14y. In developed countries, the cure rate is higher than 95% and most efforts are concentrated in improving the eye salvage rates. Strategies for eye salvage evolved from external beam radiotherapy up in the mid 1990s to chemotherapy in the present time. In the past few years, superselective intra-arterial ophthalmic artery chemotherapy (SSOAIC) has become an established therapy for retinoblastoma and although it is a complex procedure, it is now performed in many countries^[1,2]. The aim of retinoblastoma treatment is preservation of life but this technique is also remarkable in improving globe salvage^[3-6]. Published reports account for as high as 100% globe salvage in groups C and D patients and a remarkable 50% globe salvage in group E patients^[5,7]. SSOAIC has been used as primary treatment in advanced and less advanced disease (groups C and D) as well as retinoblastomas with extensive retinal detachment^[8]. It can also be indicated in bilateral cases (tandem therapy) or following intravenous chemotherapy^[9,10]. Finally it has been proposed as salvage treatment in eyes that have failed conventional treatment^[11].

Despite encouraging results were reported, some groups did not adopt this treatment and many controversies exist among treatment groups^[11]. These controversies are focused on indications; the chemotherapy agents to use; ocular toxicity and potential for long term systemic toxicity^[12-14]. These aspects seem influenced for the learning curve of this sophisticated technique and the teamwork experience^[15]. Critics to SSOAIC state that this treatment may miss occult metastatic disease which would be prevented by systemic chemotherapy, and some groups expressed their concern about retinal and choroid vascular events or drug-related

Table 1 Comparison between the 2 versions of the International Classification for Intraocular Retinoblastoma

Groups	Children's Hospital of Los Angeles version	Philadelphia version
A	Eyes with small discrete tumors away from critical structures. All tumors are ≤ 3 mm, confined to the retina, and located at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed.	Retinoblastoma tumor ≤ 3 mm (in basal dimension or thickness)
B	Eyes with no vitreous or subretinal seeding and retinal tumors of any size or location. Retinal tumors may be of any size or location not in group A. A small cuff of subretinal fluid extending ≤ 5 mm from base of the tumor is allowed.	Retinoblastoma tumor >3 mm or macular location (≤ 3 mm from foveola) Juxtapapillary location (≤ 1.5 mm to disc) Subretinal fluid ≤ 3 mm from margin
C	Eyes with only focal vitreous or subretinal seeding and discrete tumors of any size or location. Any seeding must be local, fine and limited so as to be theoretically treatable with a radioactive plaque. Retinal tumors are discrete and of any size and location. Up to one quadrant subretinal fluid may be present.	Retinoblastoma tumors with subretinal seeds ≤ 3 mm from tumor Vitreous seeds ≤ 3 mm from tumor Both subretinal and vitreous seeds ≤ 3 mm from tumor
D	Eyes with diffuse vitreous or subretinal seeding and/or massive non discrete endophytic or exophytic disease. Seeding more extensive than Group C. Massive and/or diffuse intraocular disseminated disease may consist of fine or "greasy" vitreous seeding or avascular masses. Subretinal seeding may be plaque-like. Includes exophytic disease and >1 quadrant retinal detachment.	Retinoblastoma tumors with subretinal seeds >3 mm from tumor Vitreous seeds >3 mm from tumor Both subretinal and vitreous seeds >3 mm from tumor
E	Eyes that have been destroyed anatomically or functionally by the tumor. Eyes with one or more of the following. Irreversible neovascular glaucoma, massive intraocular hemorrhage, aseptic orbital cellulitis, tumor anterior to anterior vitreous face, tumor touching lens, diffuse infiltrating retinoblastoma, phthisis or pre-phthisis	Extensive retinoblastoma occupying $>50\%$ of the globe or neovascular glaucoma Opaque media from hemorrhage in anterior chamber, vitreous or subretinal space Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber

endothelial toxicity [12-14]. These discrepancies regarding indications, chemotherapy agents to use and side effects highlight the need of a prospective multicenter study as already stated by Levin *et al* [11] but such study has not been done thus far.

Therefore, the aim of this study was to obtain information on the use of SSOAIC for the treatment of retinoblastoma by surveying groups currently using and not using this procedure in order to gain insight about the current practice about its indications, agents used and problems they have encountered.

MATERIALS AND METHODS

A survey including questions about the use of SSOAIC and the characteristics of the participating centers was prepared. An invitation to complete it was sent by email to international experts from the mailing list of the senior author based on the International Retinoblastoma Staging System working Group (www.cure4kids.org) using a dedicated link. A second announcement was made after 2wk and a third one, a month afterwards which were directed to those who were invited but did not respond the original invitation. The survey remained open for 2mo.

Since we enquired about the use of SSOAIC in different disease scenarios and classifications may vary among different groups, we used the original international classification proposed by Linn Murphree from the Children's Hospital of Los Angeles for analysis [16]. In this classification, Group E eyes are defined as those having at least one of the following features: neovascular glaucoma, massive intraocular hemorrhage, buphthalmia, phthisis, anterior segment invasion, aseptic orbital cellulitis, tumor touching lens or diffuse infiltrating retinoblastoma. However, in a modification of this grouping system by the Philadelphia group, those eyes with more than half of the retina involved by tumor but not necessarily showing the above-described

features are considered group E [17], whereas they would not qualify for group E in the original Los Angeles classification where they would be considered group D [16] (Table 1). Since this difference may affect the interpretation of the data, we asked the participants how a patient with involvement of more than half of the retina the grouping system would be classified in their institution to allow us to interpret if these patients would be considered as group D ($n=14$ centers) or E ($n=14$ centers) (no response in the remaining 3) in a given institution. Only one response per center was analyzed for this study. Responses from the same center from different doctors were compared for accuracy and in 2 cases, the respondents were contacted for clarification of their responses.

Descriptive statistical tests were used for analyzing the results. Significance tests reported are 2-tailed.

RESULTS

A total of 113 doctors were invited to participate in the survey and 79 (69.9%) from 63 centers in 35 countries responded.

Centers Using SSOAIC A total of 31 centers from 19 countries reported that they were using SSOAIC at the time of the survey. Seven (22.6%) of these centers treat more than 40 patients per year, 9 (29%) treat between 21 to 40; 10 (32.3%) treat between 10-20 and 5 (16.1%) treat less than 10 patients per year. Of these centers, 3 (9.7%) started their SSOAIC programs less than a year before the survey, from 1-3y in 15 (48.4%) and more than 3y in 13 (41.9%). Five centers (17.9%) performed less than 10 procedures, 11(39.3%) between 10 to 50, 5(17.9%) between 51 and 100 and 7 (25%) more than 100 procedures of SSOAIC. In 24 of 28 centers (85.7%) an interventional neuroradiologist performs the procedures and in the remaining 4 (14.3%) SSOAIC is done by a general interventional radiologist.

Table 2 Impact of experience in the use of superselective ophthalmic artery chemotherapy (SSOAIC)

Parameters	Groups that performed more than 50 SSOAIC applications (%)	Groups that performed less than 50 SSOAIC applications (%)	P
SSOAIC used as first line therapy for unilateral disease group E	2/12 (17)	0/17	0.16
SSOAIC used as first line therapy for unilateral disease group D	10/12 (83.3)	12/16 (75)	0.67
SSOAIC used as first line therapy for unilateral disease groups B and C	8/12 (66.7)	8/16 (50)	0.67
SSOAIC used as first line therapy for bilateral disease group D	7/12 (58.3)	5/11 (45.4)	0.24
SSOAIC used as first line therapy for bilateral disease groups B and C	4/12 (33.3)	5/16 (31.3)	1
SSOAIC used as second line therapy for uni or bilateral disease before considering EBRT	10/12 (83.3)	8/16 (50)	0.11
SSOAIC used as second line therapy for bilateral disease in eyes that received EBRT	7/12 (58.3)	1/16 (6.25)	0.004
Use of single agent melphalan as only therapy	3/12 (25)	10/16 (62.5)	0.06
Perception that SSOAIC improve the results in conservative therapy	10/11 (90.9)	9/15 (60)	0.17

EFRT: External beam radiation therapy.

Thirteen centers (46.4%) use only melphalan as single agent for SSOAIC and 4 (14.3%) use it in combination with carboplatin or topotecan whereas 11 centers (39.3%) use these 3 drugs in combination for SSOAIC.

Use of SSOAIC as First Line Treatment Twenty-three centers (74.2%) are using SSOAIC as first line therapy for cases with unilateral retinoblastoma. Two centers (6.5%) are using it for the primary treatment of Group E retinoblastoma. These 2 centers are those with largest and longest experience in SSOAIC worldwide and the creators of the technique and its modification. Twenty-two centers (71%) use SSOAIC for the first line treatment of group D unilateral retinoblastoma and 16 (51.6%) are using it for first line treatment of children with group B and C eyes in first line. For bilateral retinoblastoma, 12 (38.7%) centers use it for initial treatment of children with group D eyes, and 9 centers (29.0%) would use it for initial therapy of bilateral group B-C eyes.

Use of SSOAIC for Eyes with Relapsed –resistant Retinoblastoma After Other Modalities Eight centers (25.8%) use SSOAIC for secondary therapy of unilateral or bilateral retinoblastoma that has relapsed after external beam radiation therapy (EBRT) but for those at this situation but with a single remaining eye, 12 (38.7%) would use this modality. Eighteen centers (58%) use SSOAIC before EBRT for second line therapy of any eye failing other therapies, including bilateral cases with single remaining eyes.

Effect of Experience in the use of SSOAIC There were some statistically significant differences in the use of SSOAIC between centers with more experience (>50 applications) and those with less experience (Table 2). Centers with larger experience (>50 applications) were significantly more likely to use SSOAIC in more clinical scenarios especially for second line conservative therapy in bilateral cases.

Opinions on the Impact of SSOAIC Nineteen centers of 27 that responded the question (70.4%) stated that the use of SSOAIC improved the results in the preservation of eyes with retinoblastoma, 5 (18.5%) are not sure and 3 (11.1%) centers

reported that SSOAIC did not improve their results. These 3 centers had a trend for use of SSOAIC only for relapsed patients and use only melphalan for treatment.

Among the advantages for SSOAIC, 21 (77.8%) centers reported that SSOAIC was associated to less toxicity, 19 (70.4%) reported that it is more effective than standard therapy, 14 (51.9%) centers stated that SSOAIC improved family acceptance of treatment.

Among the disadvantages for SSOAIC, 3 centers (9.7%) reported more toxicity after SSOAIC (the same 3 centers that reported that SSOAIC did not improve their results), 10 centers reported increased cost (32.3%) and 1 center (3.2%) reported limited availability for SSOAIC therapy. Miscellaneous comments about the concerns of SSOAIC were also collected in an open question. Most included concerns about toxicity such as possibility of stroke in 4 cases, ocular toxicity in 2, risk of brain tumors as second malignancies in 1, radiation risk in 1 and anesthesia risk in 1 case.

SSOAIC use According to Geographic Location of the Centers Eleven centers (17.5%) responding this survey are in middle income countries. There were no significant differences in the use of SSOAIC compared to developed countries, however the 3 centers that had poor results with SSOAIC are from middle income countries. There was a non-significant trend for using SSOAIC as first line treatment in the USA-Japan compared to European centers that tended to prefer it for second line therapy (Table 3).

Centers not Using SSOAIC Thirty-one surveyed centers (49.2%) reported not using SSOAIC for treatment of retinoblastoma. Twenty-three (74.2%) of them were in middle or low income countries. Fourteen (45.2%) of these centers treat less than 10 patients per year, 10-20 in 5 (16.1%), 21-40 in 6 (19.4%) and more than 40 in 6 (19.4%) each year. Fifteen of 30 responses (50%) reported that they were planning to incorporate SSOAIC in their treatment of retinoblastoma and 26.7% (n=8) stated that they may consider to do so. Seven centers (23.3%) are not considering

Table 3 Patterns of use of superselective intra-ophthalmic artery chemotherapy (SSOAIC) in Europe versus the USA and Japan

Parameters	Europe (%)	USA-Japan (%)	P
SSOAIC used as first line therapy for unilateral disease group E	0/14	2/7 (28.6)	0.1
SSOAIC used as first line therapy for unilateral disease group D	8/14 (57.1)	7/7 (100)	0.05
SSOAIC used as first line therapy for unilateral disease groups B and C	6/14 (42.9)	7/7 (100)	0.01
SSOAIC used as first line therapy for bilateral disease group D	2/14 (14.3)	5/7 (71.4)	0.01
SSOAIC used as first line therapy for bilateral disease groups B and C	1/14 (7.1)	5/7 (71.4)	0.01
SSOAIC used as second line therapy for uni or bilateral disease before considering EBRT	7/14 (50)	6/7 (85.7)	0.17
SSOAIC used as second line therapy for bilateral disease in eyes that received EBRT	3/14 (21.4)	6/7 (85.7)	0.15
Use of single agent melphalan as only therapy	7/12 (58.3)	4/7 (57.1)	1
Perception that SSOAIC improve the results in conservative therapy	8/12 (66.7)	7/7 (100)	0.24

incorporating SSOAIC (3 from developed countries and 4 from developing countries).

DISCUSSION

Our survey that included most major referral centers for the treatment of retinoblastoma worldwide found that SSOAIC is used more commonly for the treatment of unilateral retinoblastoma as an alternative to enucleation in cases with advanced disease, especially in North America and Japan. One concern of the use of SSOAIC for the treatment of unilateral retinoblastoma is that children with group E disease possibly harboring occult metastasis would potentially at risk of developing clinically metastatic relapse if treated with SSOAIC [12]. Our survey detected an inconsistency in the definition of grouping of eye with retinoblastoma since half or the groups responding to our survey used the original definition proposed for a group E eye and the remaining ones used the modified version. Even though a correlation between the clinical features in eyes at the moment of presentation and the risk of metastatic disease is not absolutely clear, studies suggest that the risk of occult metastasis in eyes without glaucoma, buphthalmia, orbital cellulitis, anterior segment invasion or pthysis is less close to 0% [18]. However, this risk can be up to 10% in eyes with any of these features [18,19]. In addition, up to 17% to 24% of enucleated group D and E eyes respectively may show high risk pathology features [18]. Nevertheless, 2 centers would still offer SSOAIC to children with higher risk. Interestingly, these are the 2 centers that created and modified the technique and are those with the largest experience worldwide and reported low incidence of metastatic disease [16]. No center in a middle income country from our survey would offer SSOAIC to children with a group E eye, which probably underscores their caution to avoid any increased risk metastatic disease in such population which may be lower by enucleating these eyes and subsequently tailoring adjuvant therapy when needed.

Overall, most centers worldwide reported better tumor control with low complications in their populations regardless the center size, experience and location. Despite concerns about the toxicity of this treatment, especially to the eye,

more than three fourths of the centers reported less toxicity than other conservative treatments. The only 3 centers that reported poor results and more toxicity come from developing countries with limited experience where this modality requiring highly sophisticated facilities may be not available. Compared to systemic chemotherapy, SSOAIC is associated to milder or none hematopoietic or other systemic toxicities, but ocular toxicity including choroidal vascular changes that may adversely affect vision are of concern [12]. The mechanism and risk factors for this complication remain largely unknown, so some authors are not using this modality for low group intraocular disease.

Hence, SSOAIC is used less frequently for the treatment of bilateral retinoblastoma but according to our survey, it became the standard second line approach for those centers that have it available displacing EBRT. We found that the use of SSOAIC as second line therapy is relatively more popular in Europe where fewer centers offer it for primary therapy.

Despite of concerning reports of ocular toxicity, melphalan is the most widely used drug and the only used drug by a substantial number of centers. However, centers with more experience tended to use more drugs than those with less experience [14,20].

To conclude, SSOAIC is used in an increasing number of centers worldwide, especially for the treatment of advanced unilateral disease. However, most centers still prefer enucleation for children with group E tumors. Centers with more experience in SSOAIC use it in more clinical situations and include other drugs than melphalan in their treatment schemas. The majority of the centers using this technique report that the results improved and the complications decreased with its use. Most concerns are based on cost and availability rather than with toxicity.

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