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Research Article

Intra-Arterial Chemotherapy for Retinoblastoma: A Systematic Review and Meta-Analysis

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Abstract

Purpose: To evaluate the efficacy of intra-arterial chemotherapy (IAC) when administered in early and advanced stages of retinoblastoma and correlation between treatment response, number of IAC sessions and association of other chemotherapeutic agents to melphalan.

Methods: Comprehensive literature search of Pubmed and Cochrane Databases published between 2009 and 2019. Selection and analysis of studies were performed according to PRISMA guidelines. The main outcome was defined as the number of enucleations in early and advanced stages of retinoblastoma, according to the ICIR Classification system. Other outcomes included the number of enucleations in eyes treated with melphalan and with association of other agents, association with the number of IAC sessions performed and reported main adverse events related to the chemotherapy.

Results: From a total of 292 records obtained from the research algorithm, 41 retrospective case series were included. A statistically significant increase in the risk of enucleation was found in eyes with advanced stages of retinoblastoma (OR = 3.971; $p < 0.001$). The number of enucleation events was also independent from the number of IAC sessions performed, and the number of neutropenia events recorded during the IAC sessions. We did not find a statistically significant effect in the increased chance of enucleation of patients treated with an association of different agents (OR = 1.593; $p = 0.408$).

Conclusion: Our results confirm the efficacy and safety of IAC. Advanced retinoblastomas appear to be safely and effectively managed increasing the number of IAC sessions and adding more than one agent to the IAC sessions.

Keywords: *Retinoblastoma; Paediatric Oncology; Supra-Selective Chemotherapy; Globe Salvage; Treatment Efficacy*

Background

Retinoblastoma is the most prevalent primary intraocular tumour of childhood, accounting for 4% of all pediatric cancers and having an estimated incidence between 1/18,000 and 1/16,000 live births in the global population [1]. Retinoblastoma is associated with a mutation in the RB1 gene, responsible for tumour suppression, and is categorized whether the mutation is germline (hereditary) or non-germline (sporadic retinoblastoma). Theoretically, all cases of bilateral retinoblastoma and approximately 10 to 15% of unilateral cases carry a germline mutation. Therefore, the distinction between sporadic and hereditary retinoblastoma is fundamental as germline retinoblastomas may affect both eyes of the child, at multiple locations in the same eye and often present at a younger age (median of 15 months) [2].

In developed countries, with the contribution of emerging treatment strategies in the last decade, the survival rate approaches 98%. However, limitations in health care access in poorer countries are responsible for survival rates as low as 40% [3,4]. At present, intravenous chemotherapy (IVC) and intra-arterial chemotherapy (IAC), consolidated by focal treatments, are used as first-line treatments for retinoblastoma, and supplanted the previously strategies of enucleation and external beam radiotherapy. Both IAC and IVC have excellent therapeutic effects, presenting the advantage of disease control with globe and, sometimes, sight preservation, especially when used in earlier stages of retinoblastoma [2]. However, IVC is related to important systemic adverse events which risk is apparently reduced when performing IAC. A retrospective analysis of 64 eyes treated with IVC reported febrile neutropenia in 40% of the patients [5].

IAC was first described in 1950 by Reese and colleagues but recently streamlined by Abramson and his group at Memorial Sloan Kettering. This treatment is delivered via the internal carotid artery, providing a direct injection path of chemotherapeutic drugs (melphalan, topotecan or carboplatin) into the ophthalmic artery and thus reducing the systemic adverse events related to systemic chemotherapy while the concentration of drug delivered to the tumour site is increased. The procedure of IAC can be challenging in small children and therefore it is currently recommended in children older than 3 months and more than 6 Kg of weight. In these cases, IVC can be used until the child reaches the criteria for IAC, a treatment approach named "bridge therapy" [6]. In bilateral retinoblastoma cases IAC can be used simultaneously in both eyes, injecting different chemotherapeutic agents in each eye in the same IAC session. This process was first described by Abramson [7] and was called "tandem therapy".

However, lack of randomized controlled trials comparing IAC to IVC lead to an important lack of current scientific basis that can sustain the superiority of IAC in relation to IVC. Meanwhile, definite treatment protocols using IAC are still missing.

Purpose of the Study

The purposes of this review and meta-analysis are three; one is to summarize scientific evidence regarding retinoblastoma-diagnosed patients submitted to treatment protocols with intra-arterial chemotherapy (IAC) and to evaluate the IAC efficacy when administered in early versus advanced stages of retinoblastoma. The second is to evaluate the correlation between treatment efficacy, the number of IAC performed, and with the association of other chemotherapeutic agents to melphalan for the IAC regimen. The third is to evaluate the overall occurrence of major type of systemic adverse event, defined as grade 4 neutropenia.

Methods

Protocol and sources

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Mata-Analyses (PRISMA) guidelines. PubMed and Cochrane Library databases were searched for literature published between 2009 and 2019, combining Medical Subject Headings (Mesh) and free words using "OR" and "AND" operators. IAC was not a routinely used treatment before 2009 and the authors therefore decided on this 10-year interval period.

The search stings used in PubMed were as follows: 1) (retinoblastoma[mesh]) OR (retinoblastomas) OR (familial retinoblastoma) OR (hereditary retinoblastoma); 2) (chemosurgery) OR (chemotherapy) OR (chemotherapies); 3) (supraselective) OR (arterial) OR (intra-arterial). The final search was conducted on 15th of august of 2019.

Eligibility criteria

Randomized controlled trials, comparative nonrandomized studies and single-armed case series that included at least 6 eyes and that described efficacy outcomes, defined as enucleation rates, of intra-arterial chemotherapy performed in children diagnosed with retinoblastoma were included. Both prospective and retrospective studies were accepted (Table 1).

Two authors (GC and JP) independently reviewed the articles by reading the title and abstract. The reasons for exclusion of studies were recorded. In case of disagreement a third author reviewed the full article.

Case reports, case series with less than 6 cases and reviews were excluded. When the authors provided exclusively the Reese-Ellsworth (RE) classification system the article was also excluded do to the impossibility of performing comparisons with eyes grouped according to the International Classification of Intraocular Retinoblastoma (ICIR). When the same cohort (data reported by the same institution with an overlapping time and similar inclusion criteria) was used in different publications, the more recently published paper was selected (Table 1).

Papers including bilateral retinoblastomas were accepted as the treatment of each eye is considered independently in clinical practice. In heritable retinoblastoma, a germline mutation is present in all cells of the affected children. A second mutation needs to occur in multiple of retinal progenitor cells, resulting in multifocal or bilateral retinoblastoma. Each tumour present in heritable retinoblastoma is the consequence of the genetic susceptibility and not directly correlated with the other lesions in the same children. Therefore, our unit of measure was defined as the eye and not the patient.

Classification of retinoblastoma

Different classifications have been used in the several publications reviewed. They include RE classification system and ICIR that has 3 different versions, the Los Angeles version by Murphree., *et al*. [8], the Philadelphia version by Shields and Shields [9] and the Children's Oncology Group version. Despite the fact that the 3 versions use the same letters A to E, with A representing the smallest tumour and E the more advanced, important differences remain, especially in group D tumours. These classification differences make comparisons of treatment results less accurate. When case series provided only RE classification the studies were excluded. Studies using different versions of the ICRB system were accepted.

Data collection and analysis

Two authors (GC and JC) were responsible for data collection and revision. The variables for which data was sought were the following: number of patients and eyes included, number of unilateral retinoblastomas, median age at the first session of IAC, number of eyes classified as stage A, B or C, number of eyes classified as stage D or E, mean number of IAC sessions, number of eyes treated with melphalan alone, number of eyes treated with association of melphalan with topotecan and/or carboplatin, mean time of follow up measured in months and number of enucleations.

Two groups were defined according to the ICIR for the proposed comparisons in this metanalysis: Group A that included patients categorized as ICIR groups A, B or C, and Group B that included patients categorized as ICIR groups D and E. The number of enucleations in each group was reported. The number of enucleations in eyes treated exclusively with melphalan and in eyes treated with melphalan associated with carboplatin and topotecan were also reported.

The main outcome measure was defined as the number of enucleations in early (groups A, B and C) and advanced (groups D and E) stages of retinoblastoma, according to the ICIR system. Other outcomes included the number of enucleations in eyes treated with melphalan alone and in association with other agents (topotecan and/or carboplatin), and correlation between the number of IAC sessions performed and reported severe adverse events related to the chemotherapy, defined as neutropenia grade 4.

A meta-analysis was performed to evaluate the effect of: 1) the disease stage (group 1 - ICIR groups A, B and C and group 2 - ICIR groups D and E); and of 2) IAC performed with melphalan alone or in combination with other agents (carboplatin and topotecan); in the main outcome measure that was defined as the number of enucleations in each group. The meta-analysis was performed with the metaphor package of the R software used in R Studio environment.

The measure of effect applied was odds ratio as all the included studies had a retrospective design. A random effects model was applied in order to obtain the global impact measure, independently of heterogeneity. Heterogeneity of the sample was evaluated and quantified with Higgins and Thomson I^2 and applying the Cochran's Q test. The forest plot was used to illustrate individual results and the summary measure, and the funnel plot is presented in order to illustrate the heterogeneity between included studies.

A meta-regression was performed with the main outcome measure defined as the number of enucleations, and with following covariates: number of IAC sessions performed and safety measure defined as number of grade 4 neutropenia, in order to evaluate the independence of events in different studies. The meta-regression was performed considering the point 1 (29 studies included) and point 2 (6 studies included) analysis.

Due to the presence of null and rare events a continuity correction was applied in order to obtain measures of effect for all the included studies.

The publication bias was evaluated using the Egger test, complemented with Begg and Mazumdar test, and a Galbraith plot was obtained to illustrate the bias.

Results

Study selection and characteristics

From a total of 292 manuscripts obtained from the research applying the algorithm described above, the selection of papers was made according to the inclusion criteria. The selection process and reasons for exclusion of articles are illustrated in figure 1.

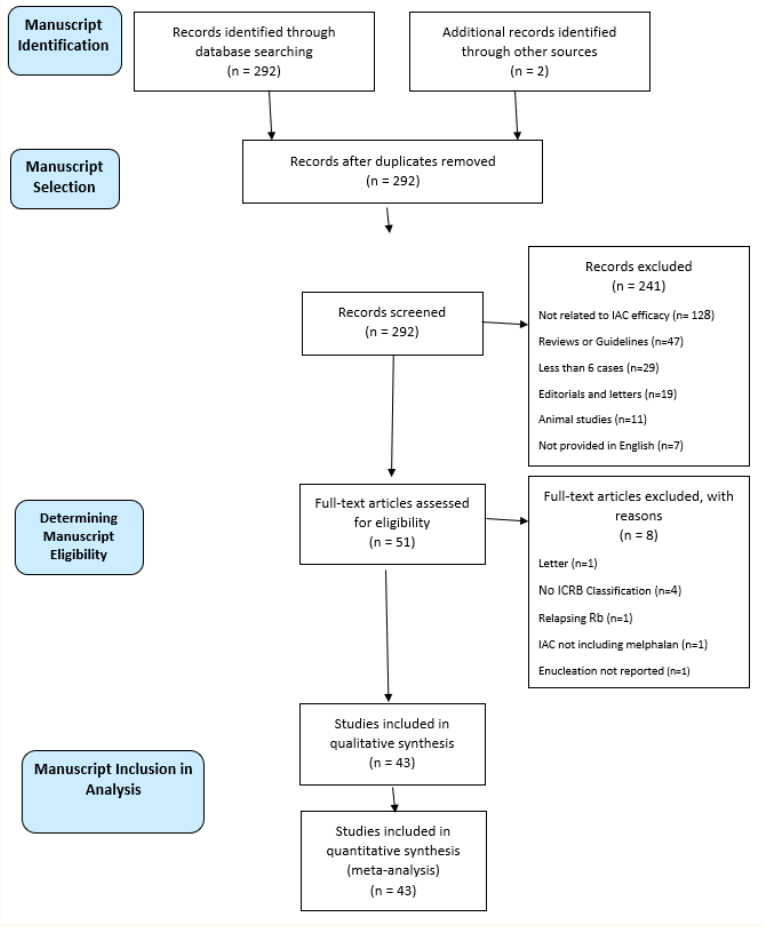

Figure 1: *Flow-chart for manuscript selection, adapted from Moher D., et al. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.*

Two-hundred and forty-one publications were excluded in the primary analysis for the following reasons: 128 were not related to IAC outcomes, 47 were reviews or treatment guidelines, 29 were case-reports or case-series including less than 6 cases, 19 were editorials, letters and comments, 11 were related to pathology or animal studies, and 7 articles were available in English.

From the 51 selected manuscripts, two of the authors (GC and JC) assessed the full text in order to collect the data for this analysis, 8 were further excluded for the following reasons: 1 was a letter, 6 did not provide ICIR Classification, 1 only included patients with relapsing retinoblastoma and 1 article did not include patients treated by IAC with melphalan.

Forty-one published manuscripts, all retrospective case series, were included in this qualitative synthesis and meta-analysis. Variables for which data were extracted in each study are provided in table 1 and 2.

Inclusion criteria	Exclusion criteria
1. Retinoblastoma managed with intra-arterial chemotherapy	1. Case reports and case series including less than 6 patients
2. Eyes grouped according to the International Classification of Intraocular Retinoblastoma (ICIR) system	2. Eyes exclusively grouped according to the Reese-Ellsworth (RE) classification system
3. Studies that provided efficacy data defined as enucleation rates	3. Use of the same cohort (data reported by the same institution with an overlapping time and similar inclusion criteria) in different publications
4. More than 6 patients included	

Table 1: *Selection criteria.*

Study author, year	Design	No of patients	No of eyes	Unilateral, No	Age, median	Eye classification		No sessions, mean	Chemotherapy regimen	
						A, B, C	D, E		Melphalan	Association
Rojanaporn., *et al*. [20], 2019	Retrospective	26	27	25	19	4	23	2,7	22	5
Wang., *et al*. [21], 2018	Retrospective	61	61	61	16	0	61	3,1	23	38
Kiratili., *et al*. [22], 2018	Retrospective	na	30	28	25,2	0	30	2,4		
Francis., *et al*. [23], 2018	Retrospective	41	64	0	?	?	?	3,6	na	na
Francis., *et al*. [24], 2018	Retrospective	na	452	165	13,4	90	293	3	na	na
Rowlands., *et al*. [25], 2018	Retrospective	84	87	48	16,8	0	86	3,5	10	76
Funes., *et al*. [26], 2018	Retrospective	81	97	na	11,4 / 14,6	13	22	4	0	97
Hua., *et al*. [27], 2018	Retrospective	62	84	40	16	0	84	5,5	0	84
Rishi., *et al*. [28], 2017	Retrospetive	10	10	10	26	3	7	3,8	0	10
Abramson., *et al*. [29], 2017	Retrospective	na	106	na	na	0	106	3,48	na	na
Francis., *et al*. [30], 2017	Retrospective	120	130	74	25,8	10	120	na	na	na
Munier., *et al*. [31], 2017	Retrospective	25	25	25	33,3	0	25	2,7	25	0
Chen., *et al*. [32], 2017	Retrospective	73	107	35	20	22	85	3,1	40	67
Tuncer., *et al*. [13], 2016	Retrospective	22	24	20	18	0	24	3	20	4
Chen., *et al*. [33], 2016	Retrospective	19	13	7	2,6	2	11	2,6	na	na

Leal-leal., *et al.* [34], 2016	Retrospective	11	11	0	22,6	2	9	3	0	11
Say., *et al.* [35], 2016	Retrospective	29	30	9	14	3	27	3	na	na
Abramson., *et al.* [7], 2016	Retrospective	60	120	48	10,92	44	76	3,46	44	76
Shields., *et al.* [36], 2016	Retrospective	49	49	49	22	6	43	3	28	21
Abramson., *et al.* [37], 2016	Retrospective	103	112	40	28,1	0	112	3	31	82
Michaels., *et al.* [16], 2016	Retrospective	17	19	17		3	16	5	11	6
Lee., *et al.* [38], 2016	Retrospective	8	8	8	28	2	6	3,25	8	0
Francesco., *et al.* [39], 2015	Retrospective	6	6	6		0	6	6	0	6
Akyüz., *et al.* [40], 2015	Retrospective	12	12	9	25,4	4	8	3	12	0
Rishi., *et al.* [17], 2015	Retrospective	6	6	6	25	2	4	3	2	4
Ghassemi., *et al.* [14], 2014	Retrospective	24	24	14	38,9	3	21	1,3	16	8
Ong., *et al.* [41], 2015	Retrospective	12	17	5	17,9	4	13	2,88	17	0
Parareda., *et al.* [42], 2014	Prospective	11	12	7	21	0	12	2,5	12	0
Shields., *et al.* [43], 2014	Retrospective	67	70	42	20	5	65	3	na	na
Hadjistilianou., *et al.* [10], 2014	Retrospective	5	5	5	11,8	1	4	3	5	0
Shields., *et al.* [44], 2013	Retrospective	14	14	3	15	0	14	3	14	0
Bracco., *et al.* [12], 2013	Retrospective	43	48	42	40	35	23	3,6	18	0
Thampi., *et al.* [45], 2013	Retrospective	16	20	6	13,3	7	13	3,1	20	0
Gobin., *et al.* [15], 2013	Retrospective	11	14	3	1,6	6	8	3,5	4	10
Marr., *et al.* [46], 2013	Retrospective	25	26	9	17,7	3	23	2	0	26
Abramson., *et al.* [47], 2011	Retrospective	67	76	60	18	17	59	na	33	43
Shields., *et al.* [48], 2012	Retrospective	8	8	7	15	2	6	1,6	na	na
Suzuki., *et al.* [49], 2011	Retrospective	343	408	199	na	165	234	3,69	408	0
Shields., *et al.* [50], 2011	Retrospective	17	17	17	20	2	15	2,24	17	0
Peterson., *et al.* [51], 2011	Retrospective	15	17	7	38,4	0	17	1,5	17	0
Abramson., *et al.* [11], 2010	Retrospective	4	8	0	10,5	4	4	2,5	2	2

Table 2: *Baseline characteristics of manuscripts included in this study.*

Synthesis of results

Enucleation rate in early (groups A, B and C) and advanced (groups D and E) retinoblastoma

From the 41 publications, 12 were not considered in this meta-analysis as only advanced retinoblastomas were reported and therefore not suitable to determine the treatment efficacy based on severity of the disease using enucleation as a measurable outcome.

The meta-analysis included 29 publications, from which 25 studies reported no "enucleation" events in at least one of the groups studied and 2 of those publications [10,11] reported no events in both groups and the remaining did not report enucleation events in the early retinoblastoma group. In these cases, a residual value of 0.5 was added to all the cells (number of events and not events in each stage) in order to obtain odds ratios, and respective confidence intervals, estimates. A random effects model was used to achieve the meta-analysis.

The heterogeneity analysis revealed that there is homogeneity between the included studies (Q_{28} = 20.806; p = 0.862; I^2 = 0.00%). However, one study [12] reported a superior effect when compared to the other studies.

We found a statistically significant effect in the increased risk of enucleation of eyes with advanced stages of retinoblastoma, when compared with patients with early stages [OR = 3.971 (p < 0.001)]. We estimate that the chance of enucleation in patients with advanced retinoblastoma is 2.793 to 5.645 higher when compared to early retinoblastoma, with 95% confidence (Figure 2).

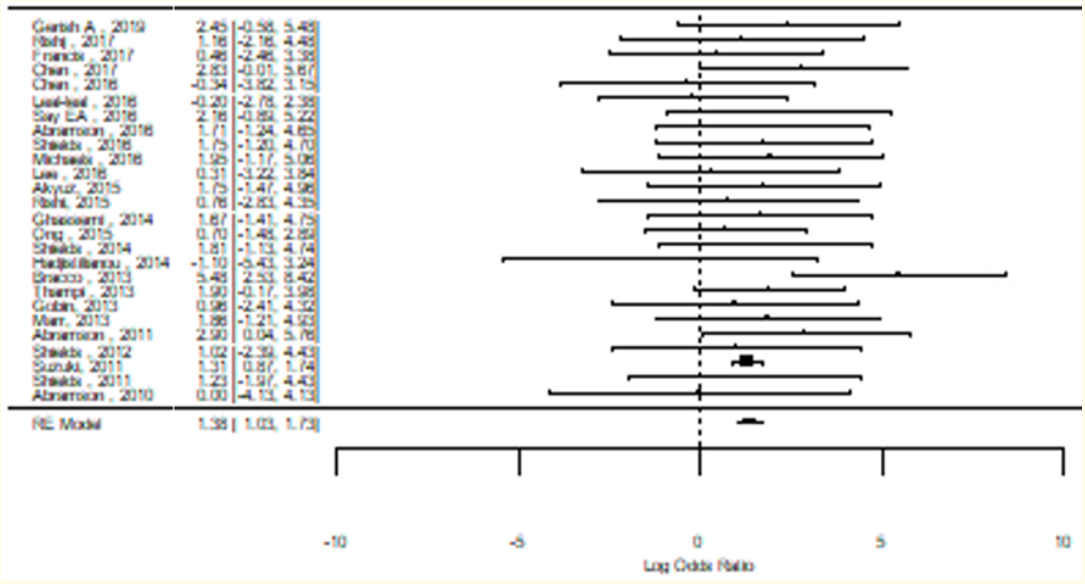

Figure 2: *Forest Plot (random effects meta-analysis) of the 26 studies that consider the event enucleation according to the ICIR stages.*

Considering the effect of the number of IAC sessions performed in each group and the reported safety events defined as grade 4 neutropenia, we evaluated the heterogeneity [I^2 = 0% and Q_{20} = 13.996 (p = 0.729)] among the studies and in the evaluation of the model [Q_2 = 0,646 (p = 0.724)] a regression coefficient of 0.514 (p = 0.422) and -0.128 (p = 0.723) were obtained for the number of sessions and

number of reported neutropenia events, respectively. We can, therefore, conclude that the number of enucleation events in each group is independent of the number of IAC sessions and of the neutropenia events.

Publication bias

The funnel plot (Figure 3) does not present a visible asymmetry, although the studies with values superior to the mean present a superior homogeneity. One study [12] reports an effect quite superior to the mean global effect, even if the standard error is similar to the other studies that report an effect superior to the mean global effect, as the study has a considerable dimension (n = 58) when compared to other studies (mean number of cases of 49, median 20, variation 5 - 399).

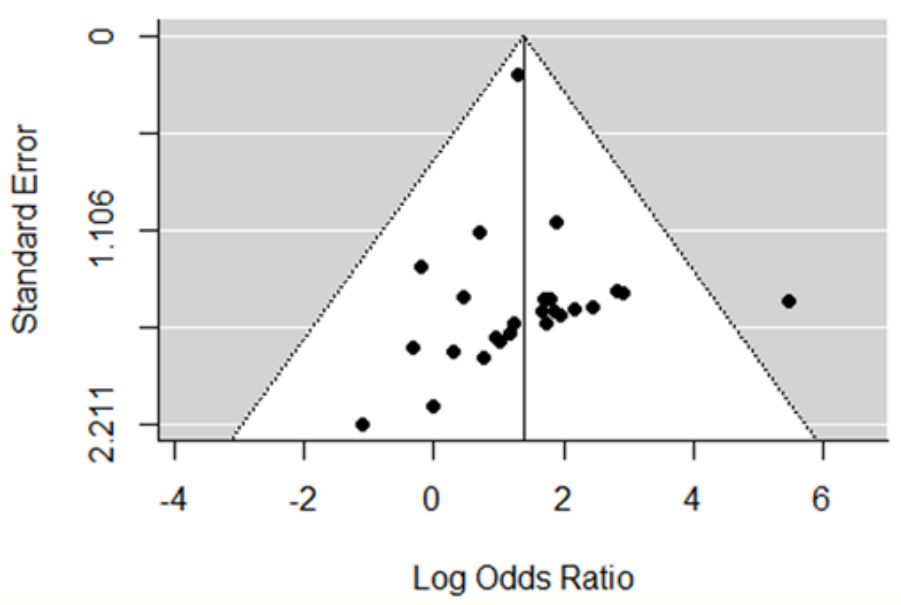

Figure 3: *Funnel plot used to evaluate the publication bias in the included studies.*

There is some evidence of publication bias, as studies with larger cohorts can report larger effects, but that bias is acceptable as the effect of the size of the study is not clearly related to the precision of the studies (Egger's test: b = - 0.064; p = 0.770; Begg and Mazumdar test: r_s = -0.385; p = 0.005).

Enucleation rate in eyes treated with melphalan and with association of other agents

From the 41 publications, 6 were used in this meta-analysis, [13-18] after excluding ones that did not include patients in the both groups considered (Figure 4).

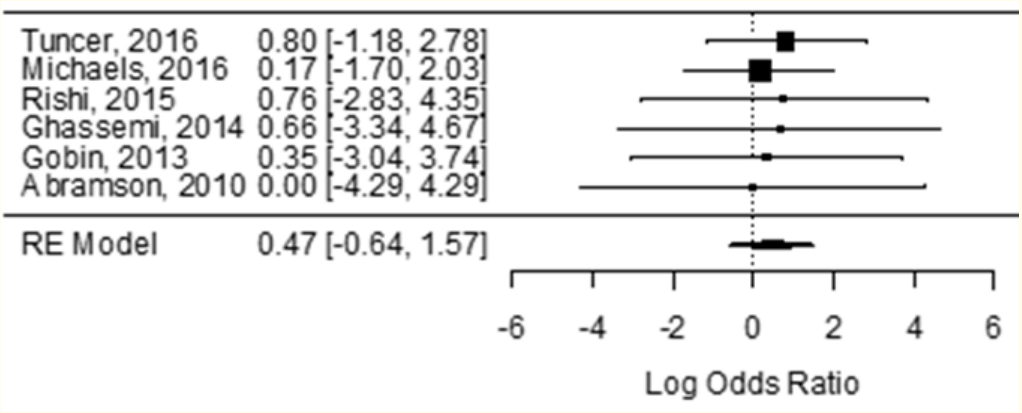

Figure 4: *Forest Plot (random effects meta-analysis) of the 6 studies that consider the event enucleation according to the use of melphalan alone or in association to other agents.*

The heterogeneity analysis revealed that homogeneity between the included studies may be assumed (I^2 = 0%; Q_5 = 0.294; p = 0.998).

We did not find a statistically significant effect in the increased chance of enucleation of patients treated with an association of agents [OR = 1.593 (p = 0.408); 95% CI: 0.529 to 4.799].

Publication bias

The funnel plot (Figure 5) does not present a visible asymmetry and either Egger's test (b = 0.003; p = 0.996) and Begg and Mazumdar test (r_s = -0.200; p = 0.719) reveal lack of publication bias.

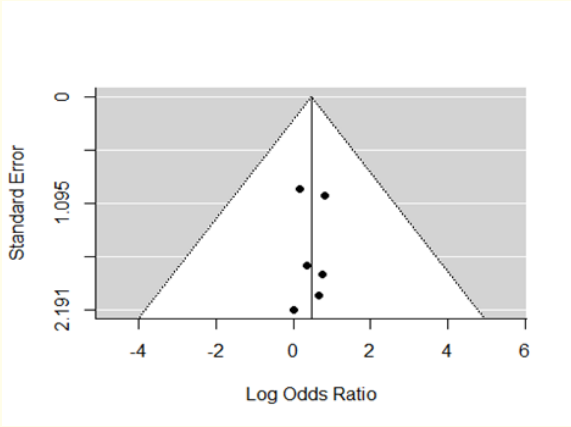

Figure 5: *Funnel plot used to evaluate the publication bias in the included studies.*

Discussion

To our knowledge this is the first meta-analysis evaluating the efficacy of single and multi-drug IAC across different stages of retinoblastoma using enucleation as a measurable outcome. Secondly, we also evaluated the impact of number of IAC treatments performed and of the major vascular events on the enucleation rate.

A previously published systematic review and meta-analysis [19] including 20 studies analyzing patients diagnosed with retinoblastoma treated by IAC, showed that 174 (11.8%) of 1467 eyes were enucleated and the occurrence of metastatic disease in 8 (1.6%) of 513 patients. They also reported globe salvage in advanced retinoblastoma in 318 (35.6%) eyes. However, this publication did not compare the enucleation rate in different stages of retinoblastoma or when using associations of melphalan with carboplatin and topotecan. Furthermore, the analysis performed lacked detail and the results were limited to pooled event rates of treatment efficacy and safety.

Another meta-analyses on this subject was published recently comparing globe salvage between intravenous chemotherapy (16 trials, 1096 eyes) and IAC (11 trials, 445 eyes) for the treatment of retinoblastoma. These meta-analyses concluded that IAC may be superior to IVC in group D patients, with a higher overall success rate and higher globe salvage this group. However, the authors could not find differences between the two treatment modalities in other stages. Despite the interesting results, this study has important limitations. Firstly, important studies previously published regarding IAC were not included and consequently the analysis only considered a limited number of eyes, which may explain limited power of the meta-analysis to extend the conclusions to other retinoblastoma stages, and possibly underestimating the efficacy of IAC. Secondly, the studies included used different classification systems that are not comparable between them, possibly compromising the accuracy of those results. Finally, the rate of adverse events were not considered, which are presumably the main disadvantage of IVC.

As expected, our study found a statistically significant effect in the increased chance of enucleation of patients with advances stages of retinoblastoma, when compared with patients with early stages, a finding never reported before. We also concluded that the number of enucleation events in each group was independent of the number of IAC sessions. Patients submitted to a superior number of IAC sessions did not have a higher enucleation rate, which suggests that increasing the number of IAC sessions is a safe and effective approach in the management of drug resistant retinoblastomas. Secondly, we did not find a statistically significant increase in risk of enucleation among patients treated with an association of agents. Based on this finding, it appears that using more than one chemotherapeutic agent during IAC is a safe alternative in the management of advanced cases or those not responding to a single agent administration.

Our meta-analysis has some limitations. We did not include studies that did not provide ICIR classification, having to exclude six publications. However, this meta-analysis still included the highest number of studies of all the currently published articles of this type. Furthermore, there still is an important lack of scientific evidence regarding criteria to guide clinical decisions in retinoblastoma as the peer-reviewed literature has no data establishing the criteria to select between single or multiple chemotherapy agents or to increase the number of IAC treatments. Therefore, a definite treatment protocol with strong scientific basis cannot be identified.

Conclusion

Our study found a statistically significant increase in risk of enucleation among patients with advanced stage retinoblastoma when compared with patients with early presentations. Furthermore, there was no increase in risk of enucleation among patients treated with multiple chemotherapeutic agents or those treated by higher number of IAC sessions. Considering the effect of the number of IAC sessions performed in each group and the potential lack of safety event defined as grade 4 neutropenia, there was no statistically significant association between the two variables. Our results suggest that increasing the number of IAC sessions and adding more than one agent to the IAC regimen are safe approaches in the management of advanced and drug resistant retinoblastomas.

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Conflicts of Interest/Competing Interests

No conflicts of interest to declare.

Availability of Data and Material

Data obtained in this project can be obtained by request to the corresponding author.

Code Availability

Not applicable.

Authors' Contributions

Data collection (GC, JP), Data analysis (GC, JC, BO, MCB), writing and review (GC, JC, BO, JM, ZC, MCB).

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