Ocular side effects following intravitreal injection therapy for retinoblastoma: a systematic review

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CRD summary
This review concluded that significant ocular complications were uncommon following intravitreal injection therapy for retinoblastoma (malignant tumour of the retina), and this risk may be reduced further by the use of careful injection technique and standard dosing regimens. These conclusions appear likely to be reliable, and the review recommendations for research are appropriate.

Authors' objectives
To describe the ocular side effects in patients receiving intravitreal injection therapy for retinoblastoma.

Searching
PubMed, Scopus, Science Citation Index, and Conference Proceedings Citation Index-Science were searched up to April 2013 with no language restrictions; search terms were reported. Reference lists of identified studies were also searched.

Study selection
Studies that reported on ocular side effects in patients receiving intravitreal injection therapy for retinoblastoma were eligible for inclusion. Studies that examined the risk of extraocular tumour spread were excluded since they were covered by a recent review by the same authors (see Other Publications of Related Interest below).

Most of the patients in the included studies were Japanese and received comparatively standard melphalan doses (8mcg to 30mcg) using a pars plana injection approach. Most studies were published between 2011 and 2013.

The authors did not state how many reviewers selected studies.

Assessment of study quality
The authors stated that study quality assessments were not performed since the identified studies were expected to be small case series or case reports.

Data extraction
Data were extracted on side effects, which were categorised as being significant or minor. Significant side effects included: vision loss, retinal detachment, treatment-limiting or sight threatening vitreous haemorrhage, cataract, chorioretinal atrophy, iris atrophy, posterior synechia, phthisis bulbi and atrophia bulbi (details on minor side effects were provided in the paper). Primary study authors were contacted for missing information where necessary.

Extracted data were reviewed by at least two reviewers.

Methods of synthesis
The proportion of patients with ocular side effects, together with 95% confidence intervals, was calculated. Results were presented by treatment dose.

Results of the review
Ten studies were included in the review (covering 295 patients and over 1,280 injections); one study included 227 patients. The mean follow-up period was 74 months (range two to 91 months).

Ocular side effects occurred in 38 patients: 17 were significant and 21 were minor. The proportion of patients experiencing potentially significant ocular side effects following standard melphalan regimens was 0.031 (95% CI 0.013 to 0.06) representing eight of 261 patients. The side effects in the eight patients included iris atrophy (three patients), chorioretinal atrophy (two patients), vitreous haemorrhage (two patients) and retinal detachment (one patient).
All eight patients were from one study (the largest study).

Of the other nine patients with significant complications: five patients experienced sight-threatening complications following dramatic dose escalations (four with melphalan, one with thiotepa); three patients experienced complications commonly associated with concurrent therapies given to these patients; and one patient had a retinal detachment.

Of the 61 patients who received intravitreal injection therapy by safety-enhancing injection techniques, all six significant side effects were either attributed to the therapeutic dose or confounded by concurrent treatments.

**Authors' conclusions**
Significant ocular complications following intravitreal injection therapy for retinoblastoma were uncommon, and this risk may be reduced further by the use of careful injection technique and standard dosing regimens. Care should be taken in the dosing of intravitreal treatments to avoid potentially irreversible vision loss.

**CRD commentary**
The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify all relevant studies in any language were undertaken by searching electronic databases and checking references. Duplicate processes were employed to reduce the risks of reviewer error during data extraction, but the methods used for study selection were not reported.

The authors' decision not to perform a quality assessment was understandable given the size and designs of the included studies; a quality assessment of the largest study would have been difficult since it was reported only as a conference abstract. Appropriate methods were used to combine data and adequate details of the primary studies were provided.

The authors’ conclusions appear likely to be reliable, and their recommendations for research appropriate.

**Implications of the review for practice and research**
**Practice:** The authors stated that intravitreal injection therapy should not be offered to patients if there was concern about their ability to be followed closely.

**Research:** The authors stated that a collaborative, multi-centre prospective study was needed to clarify the role of intravitreal injection therapy in globe-salvaging regimens through further evaluation of tumour response and analysis of potential cumulative ocular toxicity in patients receiving serial intravitreal injection therapy. The authors added that future studies should follow adverse event reporting guidelines.

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