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Localized Toxicity from Intraocular Chemotherapy in Retinoblastoma

Ramsudha Narala, MD[a], Kaitlin Kogachi, BA[a], Jesse L. Berry, MD[a,b,*]

[a]Roski Eye Institute, Department of Ophthalmology, University of Southern California Keck School of Medicine, 1450 San Pablo Street, Los Angeles, CA 90033, USA; [b]The Vision Center, Department of Ophthalmology, Children's Hospital Los Angeles, 4650 Sunset Boulevard, Los Angeles, CA 90027 USA

Keywords

• Retinoblastoma • Intraocular chemotherapy • Intravitreal melphalan • Intravitreal topotecan • Intraocular toxicity

Key points

- Use of intravitreal melphalan for vitreous seeding in retinoblastoma has allowed for stable rates of eye preservation without exposing children to external beam radiation therapy; 100% control of vitreous seeds has been reported.
- Intravitreal melphalan, although highly efficacious, is associated with ocular side effects, the most common being peripheral chorioretinal toxicity, which usually is not visually significant. Although rare, irreversible and significant ocular toxicity has been described.
- Due to melphalan-associated chorioretinal toxicity, there has been a concomitant increase in use of intravitreal topotecan, which has been shown efficacious without causing retinal toxicity, although more clinical experience is needed with this agent.
- The cause of intravitreal melphalan-related retinal toxicity remains unclear, although it may relate to pigmentation and concentration of drug in the retrohyaloid space in patients with posterior vitreous detachment.
- Optimal dosing and injection regimen of intravitreal melphalan and intravitreal topotecan remain unclear; further studies are needed to better understand the best use of this new treatment modality.

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*Corresponding author. 1450 San Pablo Street, Los Angeles, CA 90033. *E-mail address:* jesse.berry@med.usc.edu

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INTRODUCTION

In the past, treatment of retinoblastoma (Rb) involved solely enucleation and external beam radiation therapy (EBRT) for eye salvage, with serious reported side effects [1]. Over the past few decades, treatment of this cancer has focused on globe preservation therapy with chemotherapy as the foundation of any regimen. Initially, combinations of intravenous chemotherapy were used and, more recently, there has been a progression toward more localized intra-arterial chemotherapy as primary therapy.

Carl Kupfer [2] first introduced the use of intravenous chemotherapy as a form of treatment for Rb in 1953. Use of intravenous chemotherapy with carboplatin, etoposide phosphate, and vincristine sulfate for 6 cycles, however, was not routinely used until pioneered by Murphree [3], Gallie [4], Shields and colleagues [5] in the 1990s. Although there remains a critically important role for systemic chemotherapy, associated systemic side effects exist, including cytopenias, bone marrow suppression, hearing loss, and peripheral neuropathy [6–9].

In the early 2000s, the trend for globe salvage therapy moved toward the use of intra-arterial chemotherapy [10–12]. This was done to improve tumor control, particularly for advanced unilateral group D and E eyes, while decreasing systemic toxicity. Although success rates for tumor control using intra-arterial chemotherapy as primary therapy are higher than with systemic chemotherapy [13–15], the technique is more technically challenging to perform, and localized toxicity, including periocular inflammation and vascular complications, such as cerebral infarction, have been reported [16,17].

In the past several years, use of localized chemotherapy has been described as treatment of vitreous seeding. The goal of this article is to discuss the described side effects and localized toxicity of intravitreal injection as consolidative chemotherapy for seeding in Rb.

SIGNIFICANCE

Intravitreal injection of chemotherapeutic drugs for Rb has become a widely accepted consolidation therapy in the past 5 years and has revolutionized the management of vitreous seeding. The first use of intravitreal chemotherapy for Rb was by Ericson and Rosengren in the 1960s [18]. Extraocular spread of tumor cells from intravitreal injection was a concern, however, and it was quickly abandoned until 2012 when Munier [19] described a safety-enhanced technique, which involves an initial paracentesis to lower the intraocular pressure before injection to prevent vitreous reflux, followed by cryotherapy to the injection site to sterilize the needle tract. The initial report presented 30 eyes undergoing a total of 135 intravitreal injections via this described method; no eye in this study had extraocular extension. Histopathologic analysis of 5 eyes showed no evidence of spillage or tumor cell seeding along the injection tract [19].

Using the safety-enhanced approach, intravitreal injection has been found to have a very low risk of extraocular tumor spread. Suzuki and colleagues [20]