Estimation of Optimal Treatment Protocol of Methotrexate Administered by Controlled Release Implant for Intraocular Lymphoma

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ABSTRACT SUMMARY

The optimal treatment protocol of MTX for IOL by implant was estimated from a clinical perspective. The retinal permeability of MTX was calculated to be 9.25×10^{-6}cm/s for rabbit and 9.09×10^{-6}cm/s for human by comparing with *in vivo* data. The therapeutic release rate was calculated to be in the range from 0.35 to 2.8μg/hr.

INTRODUCTION

Intraocular lymphoma (IOL) refers to infiltration of the vitreous humor, retina, and choroid by malignant lymphocytes. The primary chemotherapy agent to treat IOL is methotrexate (MTX), which is the most effective drug against lymphoma cancer. IOL is initially treated with systemic chemotherapy. However, the blood-retinal barrier may necessitate higher dosage during intravenous MTX administration to achieve therapeutic levels near the retina. The high dosage of MTX increases the risk of systemic adverse effects. To avoid the systemic adverse effect and overcome the blood-retinal barrier, intravitreal therapy such as intravitreal injection and controlled release implants can be considered to treat CMV retinitis.

To maximize the therapeutic benefits, it is critical to know MTX distribution within the eye following intravitreal administration. The MTX distribution in the vitreous is obviously influenced by the rate of elimination through the retina. Thus, retinal permeability of MTX is evaluated by comparing with *in vivo* data in this study. With known retinal permeability of MTX, the optimal treatment protocol to treat IOL by controlled release implant was estimated in a human eye.

METHODS

The twelve-compartment model of the eye consists of choroid, retina, vitreous, lens, posterior and anterior chamber, iris, Ciliary processes, hyaloid membrane, Schlemm's canal, cornea, and a drug source. Fig. 1 shows the cross-section of the 3D eye model for a rabbit (Fig. 1A) and human (Fig. 1B). The most significant differences between a rabbit and human eye are the size of the lens and the volume of the vitreous. In a human eye, the lens is smaller than that in the rabbit eye. The volume of the vitreous is 4mL for the human eye, whereas 1.5mL for the rabbit eye. Half of the eye was modeled for the drug source positioned closer to the hyaloid membrane, whose symmetry plane passed through the middle of the drug source and as well as through all other eye compartments. Similarly, a quarter model of the eye was developed for the drug source positioned in the center of the vitreous. The delivered location and amount of MTX in the numerical model corresponded with *in vivo* studies (Table 1). To determine the retinal permeability of MTX, various retinal permeabilities were used to compare with *in vivo* data.

Table 1. *In vivo* studies for intravitreal injection of MTX

Model	MTX source (location)	Delivered amount	Ref
Albino Rabbit	Injection (center)	400 μg (in 32 μl)	[1]
Human	Injection (center)	400 μg (in 100 μl)	[2]

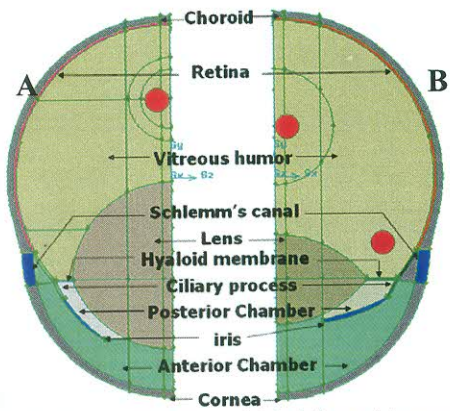

Figure 1. Eye model for rabbit (A) and human (B)

To calculate the MTX distribution by the convective-diffusive drug transport, the species mass conservation equation was coupled with the flow field.

The aqueous humor generated by the Ciliary process was modeled as a fluid source with a constant flow rate of 2.2 μL/min for rabbit and 2.5 μL/min for human. Vitreous outflow was modeled as 0.1μL/min [3] and 0.14μL/min [4] for a healthy rabbit and human respectively. The balance of the aqueous humor (aqueous outflow) was cleared through Schlemm's canal. Since the fluid properties of the aqueous and vitreous humors are nearly identical to that of water, a viscosity of 6.9×10^{-3} $g\cdot cm^{-1}\cdot s^{-1}$ and a density of 1 $g\cdot cm^{-3}$ were used.

The MTX entering the choroid from the vitreous was assumed to be cleared through the blood capillaries of the choroid. Therefore, the choroid was treated as a perfect sink for the drug passing through the choroid. Thus, the drug concentration at the outer surface of the choroid was set to zero. Because the iris, lens, cornea, and symmetrical surfaces were assumed to be impermeable to the MTX, a zero species gradient boundary condition was imposed. The diffusivity of MTX was calculated as 7×10^{-6} cm^2/s in the vitreous and 7.1×10^{-6} cm^2/s in the posterior and anterior chambers, using the Wilke-Chang correlation and the result of Tojo et al. [5].

RESULTS AND DISCUSSION

The retinal permeability of MTX was calculated to be 9.25×10^{-6} cm/s for the albino rabbit and 9.09×10^{-6} cm/s for the human by comparing the *in vivo* data (Fig. 2). The difference between regressed data of *in vivo* concentration and the present numerical result was less than 0.1%. The retinal permeability in human (pigmented mammal) was lower than that in albino rabbit. This observation was consistent with the previous studies [6] showing that drugs, which bind to pigmented retinal tissue, were slowly released. The half-life of MTX ($0.693/K_{el}$) was calculated from the slopes (K_{el}) in Fig. 2. The half-life of MTX in the vitreous was 7.1 hr for the rabbit and 13.9 hr for the human. The difference in half-lives between rabbit and human was caused by the difference of retinal permeability and the volume of vitreous humor.

Using the calculated human retinal permeability value of 9.09×10^{-6}cm/s, the numerical calculations were conducted to evaluate optimal therapeutic protocol. The range of therapeutic MTX concentration in the vitreous was from 0.23 to 2.4μg/ml to treat IOL [1]. Fig. 3 shows the variation of MTX vitreous concentration in human with different doses of intravitreal injection. For the modality by intravitreal injection, the time durations in the therapeutic range of MTX for the different doses are compared in Table 2. Fig. 4 shows the variation of MTX vitreous concentration in human with different release rates of controlled release implant for 60 days. For the modality by controlled release implant, the release rate should be in the range from 0.35μg/hr to 2.8μg/hr in order to be within the therapeutic level.

CONCLUSION

A treatment protocol for IOL administered by intravitreal injection and implant of MTX has been compared. The implant can reduce the potential toxicity and increase time duration for therapeutic range of MTX. In summary, the numerical analyses provide a useful tool for determining relevant parameter and treatment protocol for developing drug delivery strategies to treat vitreoretinal diseases.

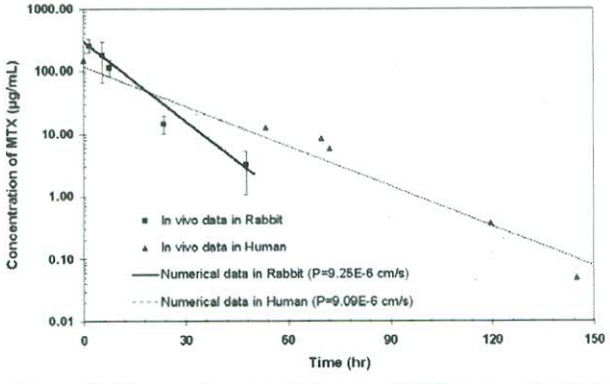

Figure 2. Comparison with *in vivo* MTX concentration between rabbit and human species

Table 2. Time duration for therapeutic range of MTX for Intravitreal injection

Injected Dose (μg)	200	400	600	800
Time (hr)	46 (66-112)	50 (80-130)	52 (88-140)	49 (93-142)

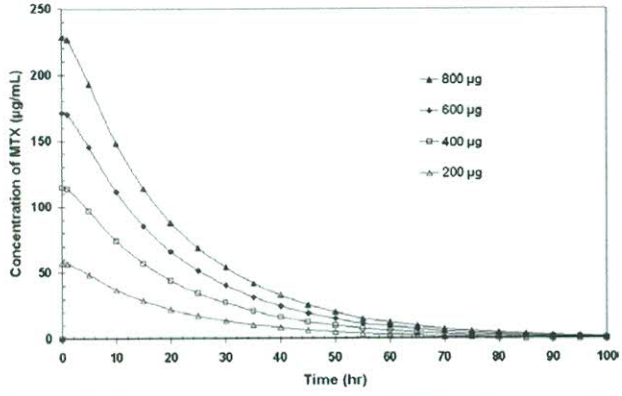

Figure 3. Vitreous concentration of MTX in human with different doses of intravitreal injection

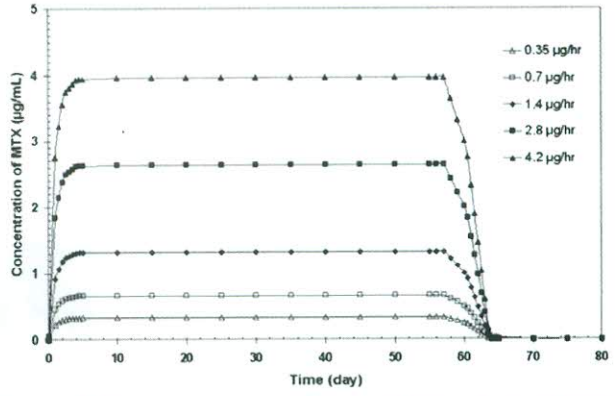

Figure 4. Vitreous concentration of MTX in human with different release rates of controlled release implant

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