How to Perform Vitreous Injection of Melphalan to Treat Recurrent Vitreous Seeding of Retinoblastoma

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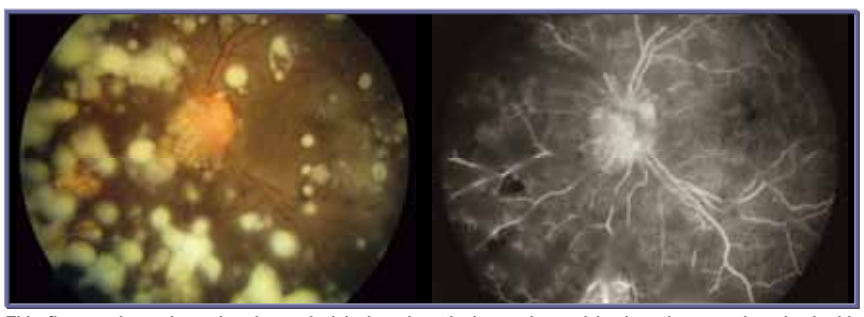
Background (1)

Vitreous seeding of retinoblastoma is one of the most important risk factors for successful eye-preservation therapy. External beam radiotherapy is the most effective method to treat diffuse vitreous seeding. However it is not rare to find recurrent vitreous seeding after the radiotherapy. The second time radiotherapy induces usually sever complications to the eyeball. Conventional modalities of eye-preservation therapy have limited effect on vitreous seeding.

Reported Success Rates of Vitreous Seeds Treatments

- **EBRT**
  - 7/41 eyes preserved (Casady JR, Radiology 1969)
- **Brachytherapy: only localized vitreous seeds**
  - only 8 eyes with localized vitreous seeds after EBRT treated with 125-I plaque among 31 and/or 42 cases. (Shields CL, Ophthalmology 1993)
  - 4 eyes of 5 treated with Iridium-192 wire. (Madreperla SA, Ophthalmology 1998)
- **Vitreous injection of thiotepa** (Ericson LA, Acta Ophthalmol 1964)
  - 0.3~0.4ml injection with 0.8mm diameter needle
  - Temporary effect of tumor regression
- **Vitrectomy after vitreous injection of thiotepa** (Seregard S, Br J Ophthalmol 1995)
  - 2mg/0.5ml thiotepa injection before vitrectomy
  - 3 eyes operated, 2 eyes preserved but lost at last

Fluorescein Angiography of Retinoblastoma with Vitreous Seeds

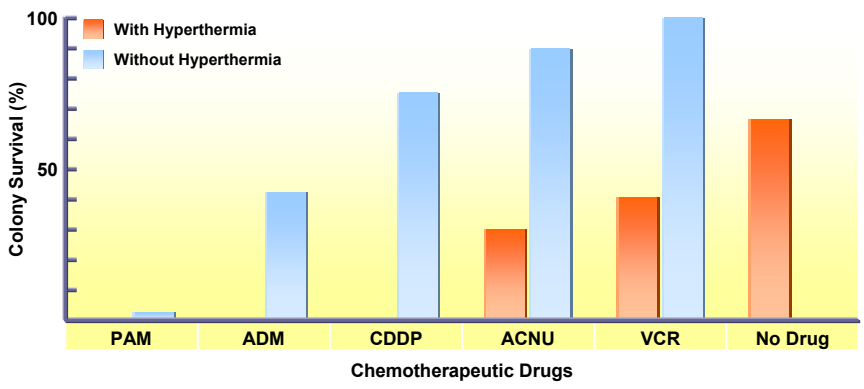


This fluorescein angiography shows decisively only retinal vesseles and implantation growth stained with fluorescein and no staining of vitreous seeds, because of poor intravitreal tranfer of the dye from the vesseles.

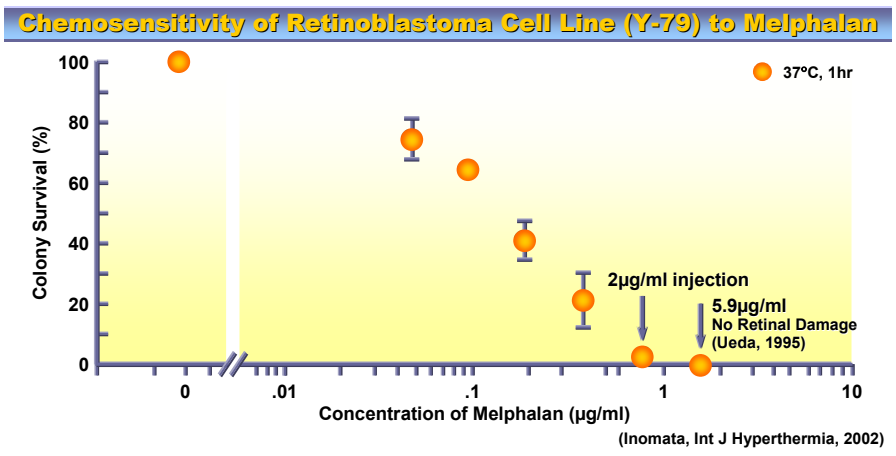
Background (2)

- Inomata, M. found retinoblastoma was the most sensitive to melphalan among 12 anti-cancer drugs. (Jpn J Cancer Res, 1987)
- Ueda, M. found ERG and the retinal structure remained unchanged after a 10μg intra-vitreal injection of melphalan in the albino rabbits. (J Jn Ophthalmol Soc, 1995)

Sensitivity of 12 Primary Retinoblastoma Cells to Chemotherapeutic Drugs With and Without Hyperthermia (42°C, 1 Hr.)



Chemosensitivity of Retinoblastoma Cell Line (Y-79) to Melphalan



(Inomata, Int J Hyperthermia, 2002)

Object

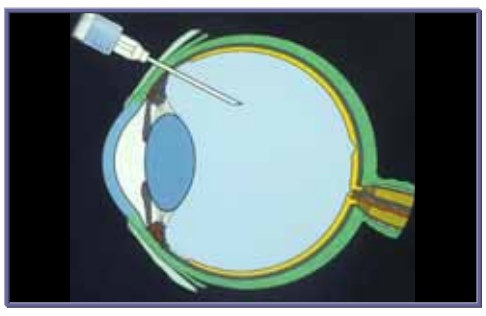
To report my new method to treat recurrent vitreous seeding of retinoblastoma by vitreous injection of melphalan

Method

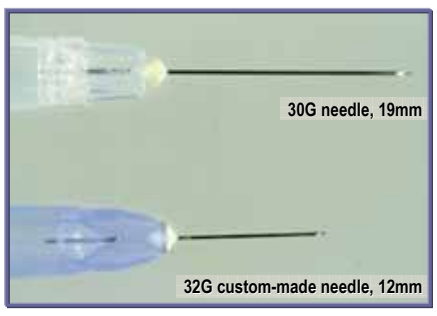
Residual vitreous seeding was treated by vitreous injection of melphalan until no active vitreous seeds were found. If necessary, it was combined with selective ophthalmic arterial injection of melphalan.

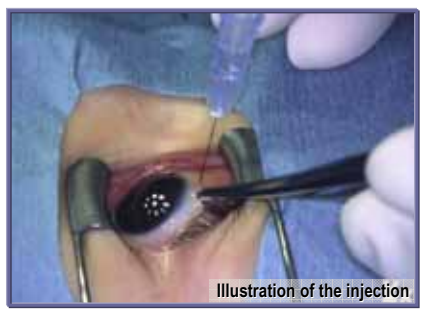
8 microgram of melphalan is dissolved into 0.2ml or recently 0.1ml of physiological saline. This concentration was determined to be safe and effective by in vitro studies. (Ref. 2, 3) A 30 or recently 32 G needle is used to prevent a needle track leakage of retinoblastoma cells. The injection site is 3 mm from the limbus which corresponds to the pars plana. Usually the injection is performed at 12 o'clock position, but if tumors are found at or near the position, another site must be chosen. Immediately after the injection, the eyeball is shaken as strongly as possible to distribute melphalan within the vitrous as much as possible. Often the ocular tension increases temporarily. The fundus examination is mandatory to check disturbance of circulation. If so, manual massage of eyeball is effective to recover the circulation.

Intra-Vitreous Injection of Anticancer Drug



Injection Needle



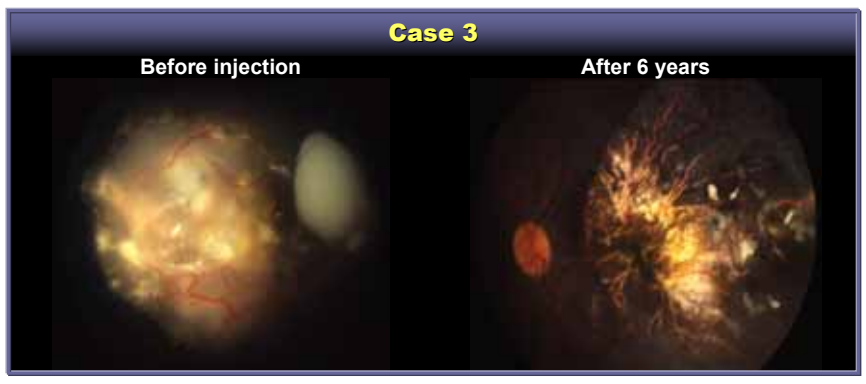


Before & After Vitreous Injection

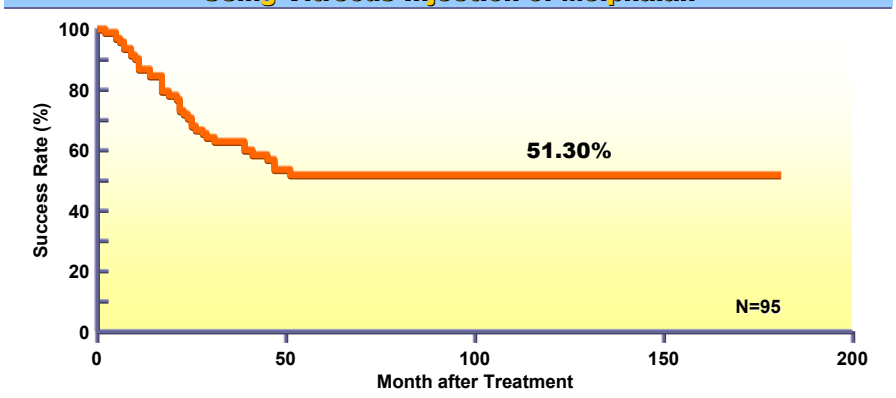
Case 1

Case 2

Case 3



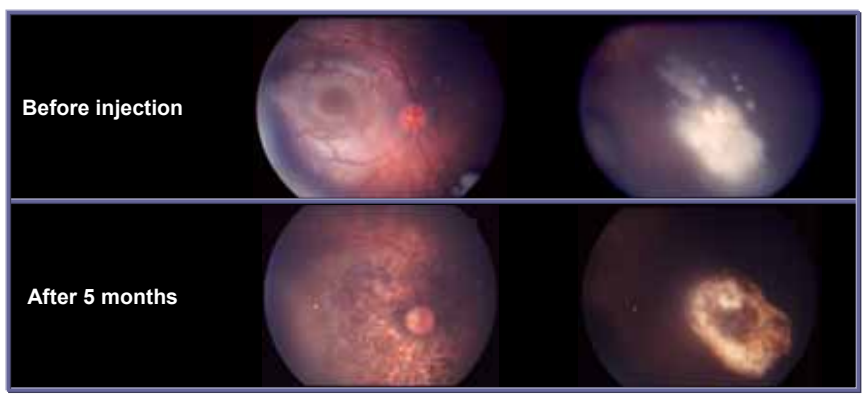
Success Rate of Eye-preservation Therapy of Retinoblastoma Using Vitreous Injection of Melphalan



Complications of the Vitreous Injection

- Diffuse chorio-retinal degeneration : 1 eye
- Slight hyperemea or subconjunctival hemorrhage around the injected site : Often
- Extraocular extension of tumor cells : None

Diffuse Chorio-Retinal Degeneration after Selective Ophthalmic Arterial Injection, TTT and Vitreous Injection of Melphalan



Discussion

- The difficulty of vitreous seeding therapy
  - Limit of effectiveness due to limited sensitivity of RTB cells to melphalan and development of drug resistance
  - Low radiation dose for vitreous base (to avoid cataract)
  - No vitreous surgery operation (Considering risk of extraocular extension of tumor cells)

Conclusion

- Intravitreal injection of melphalan is not dangerous, simple and effective to treat residual or recurrent vitreous seeding of retinoblastoma after VEC regimen chemotherapy or external beam radiotherapy.
- However the long term success rate of eye-preservation is less than 60%.
- Therefore more effective anticancer agents or treatment methods must be developed in a near future.

Acknowledgement

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References

1. Cassady JR et al: Radiation Therapy in Retinoblastoma. Radiology 93: 405-9, 1969
2. Abramson DH et al: Similutenuous bilateral radiation for advanced bilateral retinoblastoma. Arch Ophthalmol 99: 1763-6, 1981
3. Shields CL et al: Plaque radiotherapy in the management of retinoblastoma. Ophthalmology 100: 216-24, 1993
4. Madreperla SA et al: Treatment of retinoblastoma vitreous base seeding. Ophthalmology 105: 120-4, 1998
5. Ericson LA et al: Trials of intravitreal injections of chemotherapeutic agents in rabbits. Acta Ophthalmol 42: 721-6, 1964
6. Seregard S et al: Intravitreal chemotherapy for recurrent retinoblastoma in an only eye. Br J Ophthalmol 79: 194-5, 1995
7. Inomata M et al: Chemosensitivity profiles of primary and cultured retinoblastoma cells in a human tumor clonogenic assay. Jpn J Cancer Res 78: 858-68, 1987
8. Ueda M et al: Study on conservative treatment of retinoblastoma. J Jpn Ophthalmol Soc 99: 1230-5, 1995 (in Japanese)
9. Kaneko A et al: Eye-preservation treatment of retinoblasdtoma with vitreous seeding. Jpn J Clin Oncol 33: 601-7, 2003

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