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EDITORIAL

Intraocular rituximab

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Primary central nervous system lymphoma (PCNSL) is a variant of extra-nodal non-Hodgkin's lymphoma (NHL) that arises from specific sites including the brain, spinal cord, meninges, or eyes.[1] The most common ophthalmologic manifestations are vitritis and subretinal pigment epithelial infiltrates.[2–4] Intraocular involvement may be a presenting feature with subsequent central nervous system (CNS) involvement in 56–85% of patients over a period of many months to several years.[2,5,6] Conversely, about 20% of patients with PCNSL have concurrent intraocular involvement.[3,4]

Management of PCNSL is still evolving and any treatment for ocular involvement should be undertaken in conjunction with an oncologist.[4] The aim of treatment is to eradicate the ocular disease and to prevent subsequent CNS involvement. The traditional therapy with ocular radiation (40 Gy in divided doses) is ineffective in controlling the CNS disease. As the blood–brain barrier and blood–retina barrier are limiting factors that restrict drug entry into the CNS and eyes respectively, various strategies to circumvent these barriers have been developed. These include the use of high-dose systemic chemotherapy, intrathecal drug delivery, intraventricular drug delivery by a reservoir, intravitreal injections, and temporary osmotic disruption of the blood–brain barrier with intra-arterial chemotherapy infusion.[7] High-dose methotrexate (8 g/m^2) in combination with intrathecal methotrexate may not be sufficient for the treatment of ocular involvement even though therapeutic drug concentrations in the aqueous and vitreous may be achieved.[8] Intravitreal methotrexate (400 mg/0.1 ml) injected according to a standard induction–consolidation–maintenance regimen over a period of one year is effective in large proportion of cases.[9] However, complications such as cataract and vitreous haemorrhage tend to be frequent and sight threatening.[4,9]

To avoid ocular complications of methotrexate, Kitzmann, *et al*[10] have investigated the use of intravitreal rituximab and they report their initial observations in this issue of the journal.[10] The choice of drug seems to be ideal. Rituximab is a humanized monoclonal mouse antibody that targets CD20-positive B cells and the vast majority of PCNL are composed of CD20-positive B cells.[11,12] Human stem cells, progenitor cells, normal plasma cells, neurons, and glial cells in the brain do not express CD20 and therefore, are spared the effects of rituximab.[13] Rituximab is effective and is approved for the treatment of previously untreated, relapsed or refractory, low-grade or follicular lymphoma, and diffuse large B-cell non-Hodgkin's lymphoma when given systemically.[14] It has also been administered systemically as salvage therapy by itself or in combination with temozolomide as well as intrathecally for PCNSL with low neurotoxicity.[15,16] Animal studies have also indicated the absence of retinal toxicity following a single injection of rituximab.[17]

However, several issues such as dose, frequency, duration, and delivery remain to be investigated further. The dose of 1 mg/0.1 ml does provide intravitreal concentration in animal studies of more than 100 μg/ml, a level that is effective in serum and cerebrospinal fluid.[17] The half-life of 4.7 days implies that the injection should be repeated every 2 weeks rather than every 4 weeks to maintain therapeutic intravitreous levels.[17] Intraocular injection with the associated risk of potentially serious side effects (endophthalmitis, vitreous haemorrhage, retinal detachment) every 2 weeks may not be accepted by patients (especially, patients with bilateral disease) for extended periods of time. The duration of treatment, clinically identifiable end point and therefore, the total number of injections to be prescribed remain to be established. Another issue with intraocular injection is the fact that more than 40% of the injected drug is lost in the first 48 h, perhaps due to the efflux from the injection site, making this route of delivery very inefficient.[17] The use of ocular drug delivery implants or delivery pumps may overcome

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some of the issues.[18,19] Although there is some evidence to suggest that rituximab can penetrate the retina and reach the subretinal layers, its effects on lymphomatous involvement in the subretinal pigment epithelial space is not known.[17,20] Alternative routes of delivery include trans-scleral approach by subconjunctival injections.[21]

In summary, the use of intravitreous rituximab is a promising alternative to intravitreal methotrexate, but such treatment should be considered experimental at present and patients should be offered this treatment only within a framework of an investigational study.

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