The use of intravitreal rituximab in conjunction with systemic temozolomide and intravenous rituximab for the treatment of primary intraocular lymphoma

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Abstract
Primary intraocular lymphoma (PIOL) is rare malignancy affecting the eyes. It is a type of B cell malignancy, although T-cell type PIOL has been reported. PIOL is closely associated with primary CNS lymphoma (PCNSL). As many as 20% of PCNSL eventually get PIOL, while as many as 80% of PIOL patients develop CNS disease. Primary intraocular lymphoma can mimic non-neoplastic processes in the eye, such as vitreitis or uveitis. The diagnosis of PIOL is difficult. It can be performed by cytology, immunohistochemistry, flow cytometry, cytokine profiling or molecular detection of rearranged genes. The treatment of PIOL remains controversial. Some centers prefer radiation therapy, others use intravitreal chemotherapeutic injections. It is believed that the chemotherapy and radiation stop the progression of lymphoma, but does very little for preventing the development of CNS disease. In recent years, intravitreal injections gained popularity due to poor penetration of the systemic chemotherapy into the eye. Rituximab is a humanized antibody which targets CD-20 positive B cells and has been successfully used in the treatment of PIOL with minimal side effects. In this paper we present the case of a sixty year old woman who developed primary intraocular lymphoma, after treatment for her recurrent CNS lymphoma. Intravitreal injections of rituximab led to stabilization of visual symptoms and vision preservation. Currently the patient is doing well two years after treatment. We believe that further studies investigating the outcomes in patients receiving intravitreal injection of rituximab compared to intravitreal injection of methotrexate are warranted.

Key words: Rituximab, primary intraocular lymphoma, intravitreal rituximab, temozolomide

Introduction
Primary intraocular lymphoma (PIOL) is a rare malignancy that affects the ocular system [1, 2]. This disease is directly related to primary central nervous system lymphoma (PCNSL). The eyes are involved in approximately 15-25 % of PCNSL while 80% of PIOL eventually develop PCNSL [3, 4]. PIOL has been reported to be bilateral in as much as 80% of the cases [4]. The incidence of PIOL increased in the past 20 years [2, 5] and correlated well with an increased in the number of cases of PCNSL in both immunocompetent and immunocompromised patients [2, 6]. While the increase of PCNSL in immunocompromised patients can be attributed to an increase in the number of patient with immunodeficiencies, it remains unclear why the incidence of PCNSL increased in immunocompetent patients [2, 6]. Most of the PIOL cases are consistent with large B-cell non Hodgkin’s lymphoma [2,4,6-9]. However some of them can be due to clonal expansion of a T cell lineage lymphoma [10]. The malignant lymphoid cells involve the vitreous or the optic nerve head [4,9]. The diagnosis of PIOL remains a challenge mainly because the disease can mimic well non-neoplastic processes such as vitreitis or uveitis, and may respond well to steroids [11,12].

Examination of ocular fluid through immunohistochemistry, cytology, cytokine profiling, identification of molecular gene rearrangements and flow cytometry have been performed to diagnose PIOL [3,11,13].

The best treatment modality for PIOL is still controversial. In the absence of CNS disease high dose methotrexate therapy and adjuvant local radiation therapy to the eyes have been employed [14, 15]. Other clinician have used intraocular methotrexate therapy, instead of radiation therapy [16-20]. Whole brain radiotherapy (which includes parts of the posterior retina) and intravenous or intrathecal chemotherapy in conjunction with intravitreal chemotherapy [21-23] have been employed for the treatment of PIOL with concomitant PCNSL. Hormigo et al., showed that combined systemic and radiotherapy treatment increase survival for patients who present with PIOL only [24].

Rituximab is a humanized antibody targeting CD20 positive B cells [25]. It has been used successfully as intravitreal injection in the treatment of PIOL [26,27]. We are reporting the case of a sixty eight year old woman who developed intraocular lymphoma seventeen months after receiving salvage methotrexate therapy for recurrent PCNSL. Patient received treatment with intravitreal rituximab in conjunction with systemic rituximab and oral temozolomide. This treatment has shown promising results.

Case presentation
We present the case of a sixty year old woman who developed PIOL after chemotherapy treatment for PCNSL. Patient initially
presented with headache, dizziness, memory impairment, and imbalance for 5 weeks. She was diagnosed with large B-Cell CNS lymphoma by histopathological analysis after brain biopsy. She received 5 cycles of high-dose methotrexate. She went into remission for several years until her PCNSL recurred. She underwent 3 cycles of high-dose methotrexate chemotherapy between June and July. In December patient was again treated with another cycle of chemotherapy for progressive recurrent PCNSL and she went into remission. Approximately 2 years from the last treatment, the patient presented with visual impairment in both eyes. She was initially diagnosed with vitreitis and received high-dose solumedrol 1g daily for 3 days. This treatment slightly relieved the symptoms. In September, CSF flow cytometry was negative for lymphoma. In November, due to worsening vitreitis, vitrectomy on the right eye was performed and the pathology showed the presence of CD20 positive diffuse large B cell lymphoma. Following the diagnosis of PIOL, the patient was started on intravenous chemotherapy with rituximab 750mg/m2 on days 1, 8, 15, 22 for a target of 8 doses— as described in previous case reports— and Temozolomide 100mg/m2 from days 1 to 7, and days 15 to 21. In addition, the patient received intravitreal rituximab injection 1mg/0.1ml alternating in each eye from December to January. The regimen was based upon a report from a small study. Temozolomide was discontinued from day 15-21 due to the development of grade III thrombocytopenia, neutropenia and diffuse rashes. Patient recovered from neutropenia within one week after Neupogen (300 mcg) injections for 7 days. The thrombocytopenia resolved after 2 months. The patient underwent bone marrow biopsy on February due to prolonged thrombocytopenia. This test showed no evidence of lymphoma. The patient has a total of 4 rituximab systemic injections and 8 intravitreal rituximab injections. In February she underwent repeated vitreal biopsy, which showed no malignant cells.

Pathological analysis
Histopathological analysis of the brain biopsy sample showed that the tumor was characterized by large, discohesive cells with prominent nuclei and high nuclear to cytoplasmic ratio. Many of the cells were arranged around blood vessels and others were scattered in sheets within the brain parenchyma. The staining pattern for CD3 marker was negative. The staining for CD20 marker was positive. The staining pattern for AE1/AE3, CD30, GFAP, HMB45, S100, Alk1, HPL, and PLAP was negative. The tumor had histologic features indicating large B cell lymphoma. No features of anaplastic lymphoma were identified.

Imaging results
The magnetic resonance imaging of the brain, face and orbits from June 2010 showed decreased in T2 signal surrounding...
the left optic nerve and mildly increased enhancement. In November 2010 the MRI of the brain did not show any optic nerve involvement or atrophy. The April 2011 MRI of the brain, face and orbits was stable from prior studies.

Discussion

Primary intraocular lymphoma (PIOL) is a distinct subtype of the primary central nervous system lymphoma (PCNSL) [6,8] which appears in the eye and commonly presents with blurry vision and floaters [8] and less commonly presents with photophobia and pain [7,9,10,12,28,29]. This disease is commonly misdiagnosed as vitreitis or uveitis because it mimics those diseases and because it tends to respond to steroids in patients younger than sixty [4,5,8,9,12,22]. However, steroid administration fails to improve the symptoms in older patients, with a median age at sixty [4,5,8]. In patients with isolated PIOL the CSF studies may be negative [4,5,10]. Vitreous biopsy or vitrectomy with corresponding pathologic are the established methods for diagnosing this disease [4,8,22,25,29].

Our patient was initially diagnosed with vitreitis and received high dose corticosteroid therapy without improvement. Eventually, a vitrectomy with corresponding cytopathological evaluation demonstrated CD20 positive diffuse large B-cell lymphoma.

As described above the treatment for PIOL remains controversial. Patients may receive radiation therapy, systemic chemotherapy alone, systemic therapy combined with radiation therapy, or systemic therapy combined with intravitreal chemotherapy. A consensus regarding the treatment options has not yet been reached. Ocular irradiation has increased risk of cataract formation, optic neuropathy or radiation neuropathy, which in themselves are extremely disabling for the patients [14].

Due to the limited penetration of systemic chemotherapy into the eye due to blood–ocular barriers, administration intravitreal methotrexate injections in addition to salvage systemic chemotherapy became one of the preferred methods employed in the treatment of PIOL [6,7,13,17-19,30,31]. These studies indicated prolonged remission, and maintenance of visual function and minimal complications from the injections.

Rituximab has received increased attention in recent years as a useful treatment for PIOL due to decreased toxicity [11,31]. Rituximab is an monoclonal antibody which reacts against the CD20 epitope that presents on the surface of B cell lymphoma cells [25]. Intravitreal Rituximab administration has been primarily used for methotrexate resistant PIOL [26,30,31].

We decided to treat our patient with intravitreal rituximab instead of intravitreal methotrexate because we felt that the risk of receiving additional doses of systemic methotrexate could have deleterious effects on her visual apparatus. We elected to not pursue radiation therapy due to the above discussed complications. Intravitreal rituximab, coupled with oral temozolomide and systemic rituximab chemotherapy appeared to be beneficial for our patient. Following this treatment, the patient had no further visual loss, and was stable on subsequent ophthalmological evaluations. No further recurrence has been noted in this patient.

Permanent vision loss in patients with malignant nervous system tumors can be disabling and disruptive. Therefore early identification of the visual problems due to malignancy is critically important. PIOL has been closely linked to PCNSL, but it can also occur spontaneously in patients without PCNSL recurrence or de novo in patients who never experienced PCNSL [2]. PIOL should definitely be suspected in patients with vision impairment and vitreitis who have a history of PCNSL. Intravitreal rituximab injection in addition with systemic rituximab and temozolomide administration for PIOL appears to be an important new step toward treating patients. It has less side effects, improved visual symptoms control and vision preservation. To date, however, there is no consensus on the best treatment option for this disease. Therefore, new studies looking at the efficacy of rituximab as compared to methotrexate for the treatment of PIOL are warranted.

Competing interests

The authors declare that they have no competing interests.

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References


