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Combined therapy associating systemic platinum based chemotherapy and local radiotherapy into the treatment of primary intraocular lymphoma

A. Tempescul (1); O. Pradier (2); C. Marianowski-Cochard(3), JC Ianotto (1); C. Berthou (1).

1. Department of Clinical Hematology, Institute of Cancerology and Hematology, University Hospital Brest, France
2. Department of Radiotherapy, Institute of Cancerology and Hematology, University Hospital Brest, France
3. Department of Ophthalmology, University Hospital Brest, France

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Corresponding author: Dr. Tempescul Adrian
Department of Clinical Haematology
Institute of Cancerology and Hematology
University Hospital Brest
2 avenue Foch
29609 Brest cedex,
France

Phone: + 33 (0)298 22 35 04

Fax: + 33 (0)298 22 38 35

Mail: adrian.tempescul@chu-brest.fr

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Primary intraocular lymphoma (PIOL) is a very rare form of non-Hodgkin's lymphoma that is characterised by localisation in various parts of the eye, a low rate of response to treatment and a high risk of relapse, both in the eye and in the central nervous system. The diagnosis of PIOL is very difficult because of its localisation and the ways it initially manifests itself. This type of lymphoma is sometimes misdiagnosed as inflammatory uveitis and thus treated with steroids, resulting in a delay of definitive diagnosis and proper therapy. The treatment of PIOL is not standardised. Multiple regimens including chemotherapy, monoclonal antibodies and radiotherapy have been proposed, but the results thus far have been disappointing. Here, we present a group of 4 patients in which a treatment regimen combining systemic chemotherapy and local radiotherapy resulted in persistent complete remission.

Over a period of three years, we identified and treated 4 patients with PIOL. The characteristics of these patients are presented in Table 1.

The median age of patients was 73.2 years. Two patients were in relapse after a first line of treatment consisting of high dose methotrexate (i.e., GOELAMS's MBVP protocol), and two patients were undergoing their first round of this treatment.

In all patients, PIOL was diagnosed following an anatomopathological examination of a biopsy sample obtained by vitrectomy. Cytological analyses found diffuse large B cell lymphomas that were CD20 positive in all patients. The vitreous level of interleukin 10 was strongly elevated, more than 10 times the normal values, in three of four analyses. All patients underwent cerebral computed tomography with negative results, confirming that the lymphoma was localised to the eye. The patients underwent DHAOx chemotherapy, which consisted of the combined administration of dexamethasone, cytarabine and oxaliplatin. The chemotherapy was administered every 21 days, with primary prophylaxis for neutropenia provided by administration of the GCSF analogue filgrastim (5 µg/kg) from day 8 to day 12. After three cycles of chemotherapy, clinical and ophthalmologic examinations were made, and computed tomography performed; after the CT scan, consolidation therapy consisting of DHAOx chemotherapy followed by localised 3D radiotherapy was administered.

In the four patients we treated in this manner, we obtained four complete remissions. The principal adverse events due to the chemotherapy were grade 2-3 anaemia and grade 3-4 thrombopenia. No infectious or thrombotic complications were noted.

The principal adverse events due to the radiotherapy were sicca syndrome and blepharitis, both of which occurred in two patients. The symptoms rapidly regressed upon treatment with local antibiotics and artificial tears. At the time of diagnosis, the patients had received artificial implants; therefore, there was no risk of cataract due to the radiotherapy.

The follow-up examination of the patients was composed of both ophthalmological and haematological examinations.

The median follow-up time for the patients was 19.25 months, with a range of 10-28 months. At the time of writing, all four patients were alive and in complete remission.

Diagnosis of primary ocular lymphoma (PIOL) is a challenge because this disease is a very rare type of lymphoma that can arise in different parts of the eye and features a wide variety of symptoms. PIOL is considered to be a rare subtype of central nervous system lymphoma with a high risk of relapse that is characterised by either intraocular relapse or metastasis into the central nervous system (1,7). This type of lymphoma is mainly found in elderly and

immunocompromised patients and rarely in young patients (2,3). The true incidence of PIOL is not known, but its occurrence seems to be increasing (2,3).

The treatment of PIOL is not standardised. Several therapeutic approaches have been proposed, but the results are not very encouraging. Low-dose external radiotherapy results in regression of the tumour with some complications, such as retinopathy and cataract (4). Intraocular methotrexate administration could prove to be an effective treatment; however, it is an invasive procedure that can lead to complications such as keratopathy and macular oedema (6,8). Other proposed strategies include intraocular and systemic administration of rituximab (9) and classical CNS lymphoma treatment with drugs designed to cross the haemato-encephalic barrier, such as methotrexate and cytarabine (3,5). Despite this large panel of approaches, the results have been disappointing. In a very interesting study, SA Grim and colleagues identified and followed 83 patients with PIOL who were treated with various regimens. Irrespective of the type of treatment, 56% of the patients relapsed, with a time-to-relapse of 19 months (3).

In our study, the treatment consisted of induction chemotherapy consisting of cytarabine, dexamethasone and oxaliplatin (according to the DHAOx protocol)(10) followed by consolidation radiotherapy. We obtained four persistent complete remissions. Adverse events due to the chemotherapy and/or radiotherapy were tolerable.

We suggest that induction therapy according to the DHAOx protocol followed by localised consolidation radiotherapy is a potentially useful treatment for primary intraocular lymphoma.

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Nbr .	Age	Type of lymphoma	Line of treatment	Nbr of cycles	Adverse events of the chemotherapy	Radiotherapy (2 Gy/fraction)	Advers events of the radiotherapy	DFS (Months)
1	72	DLBCL	2	4	Gr 4 thrombopenia	30	Sicca syndrome, blepharitis	21
2	68	DLBCL	1	6	Gr 3 thrombopenia	30	Conjunctivitis	18
3	73	DLBCL	2	4	Gr. 4 thrombopenia	39	Sicca syndrome	28
4	80	DLBCL	1	4	Gr. 3 thrombopenia	36	Blepharitis	10

DFS - disease free survival

Table one : Characteristics of the patients treated for PIOL with combined therapy