Editorial

Lymphoma of the ocular adnexa

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Non-Hodgkin lymphomas (NHL) are malignant tumors of the lymphoid tissues which have the heterogeneous clonal expansion of lymphoid cells. Compared with lymphoma at the other sites of human body, ocular lymphomas are relatively rare. Orbital and lacrimal gland involvement are the most frequent ophthalmic sites (with bilateral involvement in 10% of patients)[1].

The intraocular lymphomas (IOL) were divided into 2 groups, internal eye lesions (vitreoretinal and uveal) and external eye lesions (ocular adnexae; OAL; including lesions of the conjunctiva, lacrimal gland, orbit, and eyelids). Most cases of IOL mainly arise from B-cell origin and almost always high grade[1]. It also can occur as AIDS-related lymphoproliferations. OALs-are mainly low-grade tumors and usually not associated with HIV infection.[2] These may have nodal involvement in 20% of patients and bone marrow involvement in 10% of patients.

The clinical features and natural history of OAL are not the same as IOL, which will bring about the different therapeutic management of both. Intraocular lymphoma is a subset of primary central nervous system lymphoma[3-4].

Although combination chemotherapy with high-dose methotrexate is the basis of treatment of primary central nervous system and intraocular lymphomas[5], radiotherapy has been the standard treatment for low-grade ophthalmologic lymphomas[6]. However, other treatment options, such as therapy with monoclonal anti-CD20 antibody, may constitute a promising alternative to external beam irradiation and its potential toxicity[7,8].

Histology of OAL[9]

Majority of published OAL cases (about 80%) were B-cell origin with half of them were marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue (MALT lymphoma). The most frequent cytogenetic abnormalities in ophthalmologic MALT lymphomas is t(11;18)(q21;q21) found 15-40% of patients. The other cytogenetics are associated with which have been observed in MALT lymphomas, such as t(14; 18)(q32;q21), t(1;14)(p22;q32), t(3;14)(p14.1;q32), and trisomy 3 and 18. These cytogenetic mainly associated with *API2* (apoptosis inhibitor 2) gene on chromosome 11q21 and the *MALT1* gene on chromosome 18q21, and the IgH promoter on chromosome 14. Other cytogenetic abnormalities, the t(3;14), trisomy 3 and 18, also have an effect on the NF-κB complex, BCL-10 and API2-MALT1 proteins, lead to the I-κB degradation and cytoplasmic to nuclear translocation of the NF-κB complex. NF-κB gene controls immunity, inflammation, and apoptosis, and may effect several genes responsible for lymphomagenesis.

Diagnosis and treatment

The initial assessment of histopathologic subtype of OAL, extension of the disease, prognostic factors, and the impact of the OAL on the eye(s) and visual function will bring optimal treatment. Radiotherapy is the main ocular adnexal lymphoma treatment, however, a few series found no difference between radiotherapy alone and combined radio/chemotherapy. Regardless of the histologic subtype of lymphoma, MALT lymphoma, and low-grade or high-grade lymphoma, radiotherapy induces

a very high local control rates from 86% to 100%, and a local recurrence rate from 0% to 15%[6,10]. However, radiotherapy may associate with immediately cutaneous or conjunctival reactions and late complications such as xerophthalmia, or cataract, or rare ischemic retinopathy, glaucoma, or xerophthalmia-induced corneal ulceration[11].

Proposed treatment guidelines are (1) Radiotherapy in patients with low-grade lymphoma who are at risk for visual impairment. In high-grade lymphoma patient, chemotherapy with or without immunotherapy can bring a rapid effect on the disease and may delay the need for radiotherapy. (2) High-grade OAL patients, apart from extension of the disease, prognostic factors, and risk for visual impairment, anthracycline-based combination chemotherapy should be selected treatment, plus anti-CD20 antibody for those CD20-positive B-cell lymphoma. (3) Low-grade lymphoma patients who are not at risk for visual impairment, various treatment options; such as radiotherapy, single-agent chemotherapy, immunotherapy with monoclonal anti-CD20 antibody, and a wait-and-see policy.

Conclusions

OAL are high proportion of low-grade B-cell NHL and approximately half of these are MALT lymphomas. Prognostic factors are like those nodal lymphoma with the same histopathologic subtype of the lymphoma. The treatments need to evaluate the impact of the tumor on ocular function, and also require concomitant ophthalmologic and hematologic management. Radiotherapy has been considered the line treatment in the patients with low-grade ophthalmologic lymphoma and no risk for visual impairment. However, monoclonal antibody immunotherapy with or without chemotherapy may be considered for high risk of disseminated or relapse. A wait-and-see policy has also been proposed in some patients with a low tumor burden of low-grade disease. The management of OAL is, therefore, a subject required the collaboration between ophthalmologists, hematopathologist and hematologists for biologic, pathologic and clinical management.

The study about OAL reported in this TSH journal showed three distinct tumor subtypes: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, or MALT lymphoma, small lymphocytic lymphoma, and diffuse large B-cell lymphoma with majority of patients in stage 1 disease, low IPI score, and satisfied treatment outcome.[12]

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