Efficacy of chemotherapy as a first-line treatment in ocular adnexal extranodal marginal zone B-cell lymphoma

E.-K. Song¹,4, S.-Y. Kim¹, T. M. Kim¹, K.-W. Lee¹, T. Yun¹, I.-I. Na¹, H. Shin¹, S. H. Lee¹, D. W. Kim¹, S. I. Khwarg² & D. S. Heo¹,3*

¹Department of Internal Medicine; ²Department of Ophthalmology; ³Cancer Research Institute, Seoul National University College of Medicine, Seoul; ⁴Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, Korea

Received 4 July 2007; revised 16 August 2007; accepted 20 August 2007

Background: Radiotherapy is commonly used as a first-line treatment for localized ocular adnexal extranodal marginal zone B-cell lymphoma (EMZBL), despite its ophthalmologic complications. This study was undertaken to analyze the efficacy of first-line chemotherapy in treating EMZBL. Chemotherapy was followed by radiotherapy only in recurrent cases.

Patients and methods: Twenty-one patients with histologically confirmed EMZBL were treated with combination of cyclophosphamide, vincristine, and prednisolone (CVP). Radiotherapy was given to CVP failure cases.

Results: CVP alone resulted in overall response rate of 100% [complete remission (CR), 76.2%]. After a median follow-up of 58 months, 14 (66.7%) of 21 cases were disease free with CVP alone, while seven cases showed disease progression, including two extra-orbital and five local failures. Radiotherapy was delivered to five local failure cases, who subsequently achieved CR with late ophthalmologic complications. There were tolerable adverse events associated with CVP.

Conclusions: Front-line CVP, in conjunction with radiotherapy in recurrent cases, is effective and well tolerated in patients with localized ocular adnexal EMZBL.

Key words: chemotherapy, MALT lymphoma, ocular adnexal lymphoma

introduction

An extranodal presentation occurs in about 40% of non-Hodgkin’s lymphoma (NHL) patients. In 5%–14% of these cases, the presentation occurs in the orbit [1]. Ocular adnexal lymphomas (OALs) are present as slowly enlarging lesions arising from the eyelid, orbit, lacrimal gland or conjunctiva. OALs are generally painless and do not compromise vision until they become large, when they can cause ptosis, proptosis, or diplopia [1, 2]. Diagnosis is made by orbital biopsy, in which a small amount of tissue is removed. Due to the difficulty of morphological classification, immunohistochemistry has become an essential approach to an accurate diagnosis. Most OAL patients are classified as having indolent NHLs. Indolent NHLs include extranodal marginal zone B-cell lymphoma (EMZBL) of the mucosa associated lymphoid tissue (MALT; the most common subtype) and follicular or small lymphocytic lymphoma. On the other hand, diffuse large B-cell lymphoma (DLCL) makes up a considerable portion of aggressive OALs [1]. Low-grade OAL carries a better prognosis than high-grade one. When confined to the orbit, indolent NHL can most often be cured with radiotherapy. Radiotherapy confers a high rate of local control with long-term efficacy [3, 4]. However, radiotherapy commonly leads to acute ophthalmologic toxic effects, such as moderate cutaneous or conjunctival reactions, as well as late complications such as constant cataract, xerophthalmia, rare ischemic retinopathy, glaucoma or corneal ulceration. In addition, disseminated relapses after radiotherapy have been reported in 17% of patients (range, 6%–50%) [4].

Patients with disseminated or high-grade OAL usually receive single-agent or cytotoxic combination chemotherapy [4]. However, several chemotherapy trials have been restricted to only a small portion of low-grade OAL patients [4–6]. Accordingly, we sought to examine the efficacy of cyclophosphamide, vincristine, and prednisolone (CVP) combination therapy as a first-line treatment for localized ocular adnexal EMZBL.

patients and methods

patients

Fifty-four patients had been newly diagnosed with ocular adnexal EMZBL in Seoul National University Hospital from 1990 to 2004. Thirty-one
patients received local treatment (eight, excision only; and 23, radiotherapy alone) and 23 had combination chemotherapy as a first-line treatment. Of 23 patients who received chemotherapy, CVP was given to 21 patients with localized (or bilateral) OAL but combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone was given to two with disseminated OAL (one with cervical and one with mediastinal lymph node involvements). More intensive chemotherapy was administered to disseminated OAL cases, due to poor prognosis in case of extra-ocular involvement at the diagnosis [4]. Overall, 21 patients with localized disease and ocular adnexal presentations were included in a retrospective study. A staging work-up was carried out based on physical examination, review by an experienced ophthalmologist (SIK), chest radiograph, magnetic resonance imaging (MRI) of the orbit, computed tomography (CT) of the chest and abdomen, and bone marrow aspiration and biopsy.

**treatments**

CVP chemotherapy consisted of cyclophosphamide (1000 mg/m² i.v. >30 min) on day 1, vincristine (1.5 mg/m² (maximum 2 mg) i.v. bolus) on day 1, and oral prednisolone (40 mg/m²) on days 1–10. Treatment cycles were repeated every 3 weeks in an outpatient clinic. All patients were scheduled to receive six cycles of CVP, assuming no disease progression or substantial toxicity. Patient who had suffered recurrence or progression after CVP required supplementary radiotherapy at a dose of 30 Gy. After three and six cycles of CVP, all patients underwent disease reassessment by physical or ophthalmologic examination, along with a CT or MRI scan of the affected area. Response to CVP was assessed according to international workshop criteria [7]. Complete remission (CR) or CR-unconfirmed status was designated as a CR. Adverse events were graded using the National Cancer Institute–Common Toxicity Criteria (version 2.0).

Patients were reassessed after completion of CVP treatment every 3–4 months for 1 year, then biannually for 3 years, and then annually. Tests at follow-up visits included history, ophthalmologic/physical examinations, complete blood cell count, and lactate dehydrogenase (LDH) level. An additional CT/MRI scan of the orbit was carried out as appropriate.

**statistical analysis**

The study end point was the overall response rate after CVP in all patients or CVP followed by radiotherapy in recurrent cases. Other end points entailed adverse events and progression-free survival (PFS). PFS was measured from the start date of CVP to the date of disease progression, relapse, or last follow-up visit. PFS curve was obtained using Kaplan–Meier method [8].

**results**

**patients**

The clinical characteristics of the 21 patients are listed in Table 1. Median age of our patients was 59 years with a male–female ratio of 2.5 : 1. Twelve (57.1%) of 21 patients presented with unilateral periorbital swelling, while the remaining patients had foreign body sense due to an orbital mass, proptosis, visual impairment, dryness, and exophthalmos. Primary sites of OAL were as follows: periorbital soft tissues (n = 8); conjunctiva (n = 6); eyelid (n = 5); lacrimal gland (n = 2). Only two patients had bilateral OAL (one in both eyelids; and the other in both lacrimal glands). These two patients were staged as Ann Arbor IIE. No patients had B symptoms. Elevated LDH level was observed in only 1 (5.3%) of the 19 patients tested. All patients had good performance status (Eastern Cooperative Oncology Group 0, 20 patients; and 1, one patient). Hepatitis C virus (HCV) tests were negative in 11 tested patients.

**treatment outcomes**

Of the 21 patients initially treated with CVP, 16 (76.2%) and 5 (23.8%) patients achieved CR and partial remission (PR), respectively (overall response rate 100%). After a median follow-up of 58 months (range, 5–163 months), recurrence or disease progression was observed in 2 (12.5%) of the 16 CR patients and in 5 (100%) of the five PR patients. As shown in Table 2, five of seven patients with relapse or progression received second-line radiotherapy. Each of these five patients achieved CR. However, two patients were lost to follow-up and received no additional therapy.

One patient, who had achieved CR after initial CVP, relapsed 160 months after CVP. The cancer had spread to the cervical and abdominal lymph nodes. At that time, his pathologic diagnosis from disseminated sites was DLCL subtype.

Except for two cases lost to follow-up, 19 patients treated with front-line CVP, or in combination with radiotherapy in

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients available</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Range</td>
<td>29–79</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>15 (71)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6 (29)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>No</td>
<td>21 (100)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lactate dehydrogenase level</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Normal</td>
<td>18 (95)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Elevated</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>IIE</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>IE</td>
<td>19 (90)</td>
</tr>
<tr>
<td></td>
<td>IIe</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Performance status</td>
<td>0</td>
<td>20 (95)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>12 (57)</td>
<td></td>
</tr>
<tr>
<td>Periorbital swelling</td>
<td>5 (24)</td>
<td></td>
</tr>
<tr>
<td>Foreign body sense</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Proptosis</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Dryness</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Anatomic location</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Orbit</td>
<td>8 (38)</td>
<td></td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>6 (29)</td>
<td></td>
</tr>
<tr>
<td>Eyelid</td>
<td>5 (24)</td>
<td></td>
</tr>
<tr>
<td>Lachrymal gland</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Both orbital adnexa</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Characteristics of 21 patients with ocular adnexal lymphoma of mucosa associated lymphoid tissue type
the event of recurrence, showed no evidence of disease at the time of analysis. Fifteen (66.7%) of 21 cases were still disease-free with chemotherapy alone, with a median PFS of 55 months (range, 4–99 months). With chemotherapy alone, the 2-year and 5-year PFSs were 90% and 66%, respectively, while median PFS was not reached (Figure 1). Median PFS in the relapse or progressive group was 29 months (range, 12–160 months). There was no connection between the site of involvement and treatment outcomes, including response to CVP, relapse or progression, and survival.

**adverse events**

Six cycles of CVP were administered without significant toxic effects, except in three cases. One patient in PR after three cycles of CVP progressed, one in PR was lost to follow-up after four cycles, and one in CR refused further chemotherapy after five cycles and eventually relapsed 22 months after CVP. As a result, patients received a mean of 5.7 cycles of CVP. Toxic effects associated with CVP treatment are briefly summarized in Table 3. Hematologic toxicity occurred in 14 patients (mild to moderate neutropenia, n = 13; grade 1 anemia, n = 1). Nine (42.9%) of 21 patients developed grade 1 neutropenia. No cases developed a grade 3 or 4 adverse event, neutropenic fever, or thrombocytopenia. Furthermore, only two patients developed grade 1 non-hematologic toxic effects. One patient showed elevated alanine aminotransferase while another patient developed peripheral neuropathy. Late ophthalmologic complications in patients treated with additional radiotherapy included xerophthalmia (n = 2) and cataract (n = 1).

**discussion**

Our study indicates that front-line CVP treatment is effective and generally well tolerated. Most toxicity was found to be mild to moderately severe in patients with localized ocular adnexal EMZBL. In addition, radiotherapy can be reserved for recurrent or progressive disease.

OAL is the most common primary orbital malignancy, accounting for up to 55% of orbital malignancies [2, 9, 10]. Although OAL primarily localizes to the orbit, a systemic staging work-up is necessary for OAL, since ~15% of patients with localized disease had systemic involvements [2, 4]. Here, extra-orbital involvements were rarely observed at the time of diagnosis. OAL representing slowly enlarging lesions could debilitate visual acuity [4]. However, most of our patients presented with unilateral periorbital swelling, while only two
patients had an impaired vision. Although a previous study has indicated a potential association between OAL of MALT type and HCV [11], such a correlation was not confirmed in our series. Our patients had good performance status, normal LDH levels (except one case) and no B symptoms, consistent with previous findings [5, 10, 12, 13]. Although many studies have shown that OAL is more common in female patients [4, 6, 10, 13–16], we observed a male–female ratio of 2.5 : 1. This is consistent with studies of other Asian populations [3, 5, 12]. Further studies of the geographic variations in male:female OAL patient ratios are warranted.

Regarding prognostic factors, high-grade or disseminated OAL showed poor outcome [4, 10]. Because our patients presented with low-grade and localized OAL, clinical features should be investigated as a prognostic factor. Recent study has shown that lymphomas involving the lacrimal gland or eyelid have a higher risk of dissemination and lymphoma-related death, as compared with those involving conjunctiva or deep orbit. Additionally, bilateral orbital involvement, optic neuropathy, or pain was associated with an increased risk of tumor-related death [17]. However, we did not find any relationship between the site of involvement and treatment outcome in the present study.

In terms of treatment modality, radiotherapy has been widely adopted as an initial treatment for OAL of MALT type [4]. Radiation dose ranging from 28 to 36 Gy for indolent OAL or from 30 to 51 Gy for aggressive OAL has been typically given [3, 14, 18] at a recommended dose of 30 Gy for ocular adnexal EMZBL [12–14]. This is consistent with our study. Despite the prominent local control of tumor [10, 12–14], radiotherapy had the disadvantages of ophthalmologic complications: skin irritation (78%) or mild conjunctivitis (16%) [12]; lens toxicity (26%) [14]; corneal complications (19%) [14]; xerophthalmia (14%–35%) [10, 14, 15]; retinal complications (4%) [12]; and cataract (10%–53%) [10, 12–15]. Moreover, frequent systemic relapse has been perplexing [4]. Consequently, alternative treatment modalities have been under consideration, including antibiotic therapy [16, 19, 20], wait-and-see [21], chemotherapy [6], and rituximab [22, 23].

Here, CVP alone showed a high response rate and favorable survival outcome, comparable to other studies [4, 10, 13, 15]. Furthermore, CVP was well tolerated, while additional radiotherapy provoked late ophthalmologic complications such as xerophthalmia and cataract. After CVP alone therapy, relapse most commonly occurred locally (five of seven relapse patients) and typically occurred within 43 months. Interestingly, one patient relapsed to systemic lymph nodes 160 months after CVP treatment. Considering frequent extranodal relapses in OAL [13] and the very late relapse in this patient, it was not clear whether systemic relapse was second de novo DLCL or transformed DLCL from low-grade OAL.

Although therapy-related myelodysplastic syndrome (t-MDS) or acute myeloid leukemia (AML) can occur after treatment of NHLs with alkylating agents [24, 25], administration of cyclophosphamide was associated with a non-significant 1.8-fold risk of t-MDS/AML [25]. In addition, t-MDS/AML risk after high-dose chemotherapy followed by stem cell transplantation was significantly increased compared with conventional chemotherapy in indolent NHL [26]. The risk should be balanced with side-effects of other treatment options for the disease. Consequently, CVP alone may be substituted for radiotherapy as first-line treatment for OAL of MALT type.

Future efforts should be directed towards reducing failure rate by adding rituximab to CVP, because patients treated with rituximab and chlorambucil did not relapse, unlike those treated with rituximab alone [22, 23]. However, it takes a longer follow-up period to conclude the long-term efficacy of rituximab and chlorambucil. Recently, *Chlamydia pitiui* (Cp)-eradicating antibiotic therapy has shown slow and gradual response either in Cp-positive or in Cp-negative OAL, suggesting the possibility of disease control without complications [16, 19]. Contrarily, no effect of blind anti-Cp doxycycline has been found in a previous study, possibly due to a geographic difference in the role of Cp [20]. Considering the small sample size and short follow-up periods examined in the study, it is difficult to consider anti-Cp antibiotic therapy as a standard treatment for localized OAL at the present time [4, 16, 19, 20].

Although local radiotherapy or single-agent chemotherapy has been usually administered, OAL has shown low dissemination (3%–7%) or transformation (0%–4%) [5, 6, 12, 13]. In our series, recurrent cases showed locoregional progression only and well managed with additional radiotherapy. Only one case showed high-grade lymphoma after 160 months in CR state. However, it was not clear whether it is de novo or transformed high-grade lymphoma. Based on these findings, first-line CVP combination chemotherapy, in conjunction with radiotherapy in recurrent cases, is effective and well tolerated in patients with localized ocular adnexal EMZBL.

**funding**

Korea Health 21 R&D Project; Ministry of Health & Welfare; Republic of Korea (0412-CR01-0704-0001).

**acknowledgements**

The authors have no potential conflicts of interest.

**references**