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Full Length Article

Outcome of primary orbital lymphoma treated with induction chemotherapy followed by conformal radiotherapy

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KEYWORDS

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Abstract *Purpose:* To analyze the clinical outcome of primary orbital lymphoma (POL) patients treated with a combined modality approach with local radiotherapy after induction chemotherapy.
Methodology: We retrospectively retrieved demographic, treatment and outcome data of patients treated for POL from 2000 to 2010. The charts were reviewed and the data were tabulated in a pre-designed pro-forma.
Results: 23 patients of POL were found evaluable. Median age was 55 years (range 24–70 years). Of 23 patients, 15 were male and 8 female, making the male:female ratio approximately 1.9:1. Patients were thoroughly evaluated and staged. All but one patient received multi agent chemotherapy. Radiotherapy was delivered for all cases. Radiation was delivered by 3DCRT technique. Median dose of radiation was 45 Gy (range 20–45 Gy). Median follow up was 26.8 months. None of the patients had any evidence of local failure or systemic progression.
Conclusion: A combined modality therapy with a combination of CHOP/COP based chemotherapy and moderate dose of radiotherapy imparts excellent long term local and systemic disease control.

Introduction

Primary orbital lymphoma (POL) is an uncommon extra nodal lymphoma, accounting for 8% of all extra nodal NHL and 1% of all NHL [1,2]. It makes up 10% of all orbital tumors [3]. Maltoma has been reported to be the commonest type of NHL in POL. However, diffuse large B cell lymphoma (DLBCL) and marginal zone lymphoma (MZL) have also been reported in a different series [4]. POL has been reported to be a slow growing tumor and mostly remains confined to the orbit only. However, neglected cases may erode the bony barrier and spread to the adjacent organs. Over the years a moderate dose of radiation has remained the most effective form of therapy for such tumors with excellent disease control [5,6]. The role of chemotherapy and antibiotics has evolved over the past decade [6]. The introduction of multi agent

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chemotherapy followed by radiation is being considered the new standard and expected to improve survival further. Here, in this report we intend to present the treatment outcome of POL patients treated with a combined approach of radiotherapy and chemotherapy.

Methodology

Patients

We retrieved the demographic and treatment data of patients treated for POL from 2000–2010. The charts were reviewed and the demographic, treatment and outcome data were retrieved using a predesigned pro-forma.

Pretreatment workup

All patients were evaluated by a team of radiation and medical oncologist in our multidisciplinary clinic. A contrast enhanced computed tomography (CECT) scan of the head, face and neck, thorax and abdomen was advised. Bone marrow aspiration, touch preparation and biopsy were performed to stage these cases and confirm the diagnosis of POL. A post chemotherapy CECT scan was performed to assess response to induction chemotherapy. A MUGA scan or 2D echocardiography was performed to assess the pretreatment left ventricular ejection fraction.

Radiation therapy

For all radiation treatments, patients were immobilized in a thermoplastic immobilization device in the supine position with arms by the side of the patient. For planning with conformal radiation technique (three dimensional conformal radiation therapy, 3D-CRT) planning CT scan was acquired (with intravenous contrast) with a 3 mm slice thickness on Philips large bore CT scanner. Treatment was delivered with 6 megavoltage photons on CL 2300 CD (Varian Medical System, Palo Alto, California, United States). The gross tumor volume (GTV) was defined as the tumor evident on the planning CT scan. The whole orbit was considered as the clinical target volume (CTV). The CTV volume was restricted with respect to natural barriers such as bone. CTV was expanded by isotropic 3–5 mm expansion for generating planning target volume (PTV). The dose prescription ranged from 36–45 Gy at 1.8–2 Gy per fraction. Patients with a complete response (CR) received 36 Gy and for less than a CR 45 Gy. During radiotherapy planning the highest priority was given to achieve conformal dose distribution covering the PTV followed by maximal sparing of the contralateral eye and optic apparatus (Fig. 1).

Chemotherapy

Multi agent chemotherapy with a combination of cyclophosphamide, vincristine, and prednisolone (CHOP/COP) with or without Adriamycin was prescribed for four cycles and repeated every 3 weeks. Adriamycin was added for intermediate grade histology only.

Assessment of toxicity and follow up

Acute toxicities were assessed as per acute radiation morbidity scoring of radiation therapy oncology group (RTOG). All patients were assessed weekly during radiation therapy. After the completion of treatment, patients were evaluated at 1 month and then every 3 months for first 2 years and 6 monthly in subsequent years. Clinical examination was performed at each follow up and imaging (CT/MRI) was done

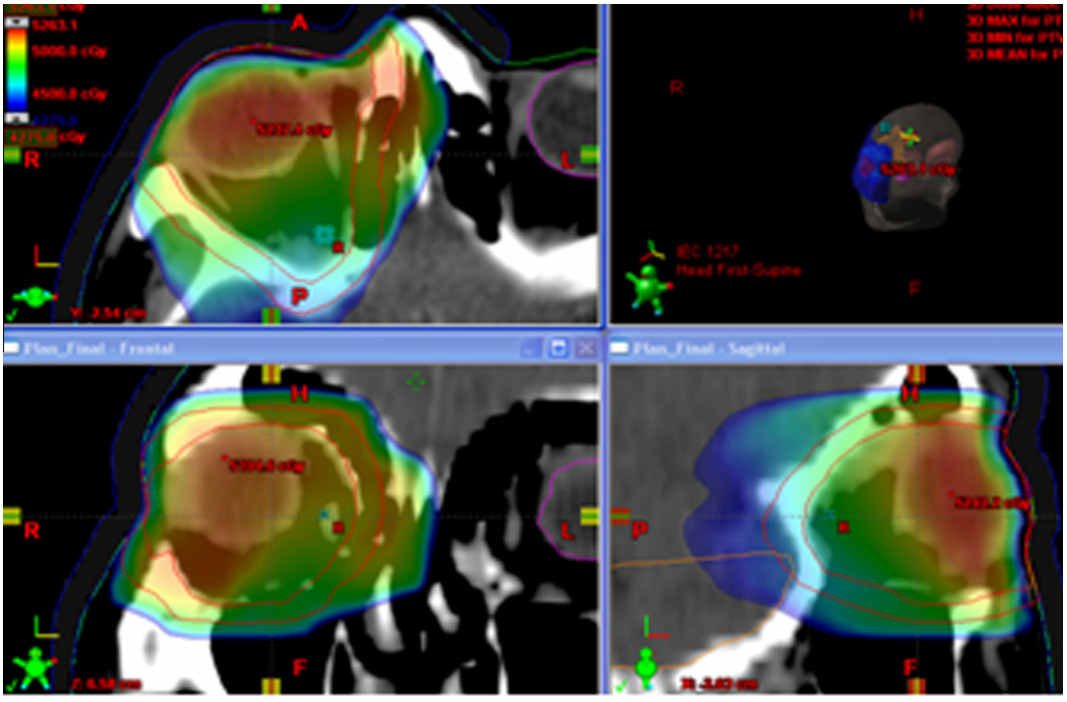

Figure 1 Images depict target delineation, dose color wash in a case of orbital lymphoma.

every 4–6 months or earlier in the case of clinical suspicion of progression.

Clinical outcome end-points and statistics

Disease free survival (DFS) for primary treatment was defined as from the start of first treatment to the diagnosis of recurrence. However, in the absence of any event the statistical analysis was not possible.

Results

Patients

23 patients of POL were found evaluable. Median age of the cohort was 55 years (range 24–70 years). Of 23 patients, 15 were male and 8 female, making the male:female ratio approximately 1.9:1. Proptosis ($n = 23$) was the commonest symptom followed by decreased vision ($n = 8$), epiphora ($n = 2$), and pain ($n = 1$). CECT scan of the face was the commonest radiological investigation performed in 19 patients. The CECT scan revealed a moderate to strongly enhancing mass in the intra or extraconal compartment with invasion of extra ocular muscles. Bone erosion and extension to the para nasal sinus was noted in 2 patients. An MRI of the orbit was performed in 8 patients. MRI revealed a hyper intense mass on T2 weighted images in the conal compartment with a variable extent of involvement of the extra ocular muscle (Fig. 2). All patients had unilateral involvement. The median symptom duration was 16 months. Complete staging workup including detailed radiological examination, bone marrow aspiration and bone marrow biopsy was performed for all cases. 18 patients were staged as stage IAE and stage IAXE was noted in 1 patient. 2 patients each had stage IIAE and stage IIIAE respectively. Low grade B cell lymphoma was the commonest histology found in 10 cases, followed by DLBCL in 7 cases. Three patients had small cell lymphoma, 2 patients had maltoma and 1 patient had MZL.

Chemotherapy

All 23 but one patients received combination chemotherapy. Eight patients received CHOP chemotherapy whereas 14 patients received COP chemotherapy. The median number of chemotherapy cycles used was 4 (range 4 to 8). Only 5 patients achieved a CR after the planned chemotherapy schedule. All other patients achieved a partial response and near complete

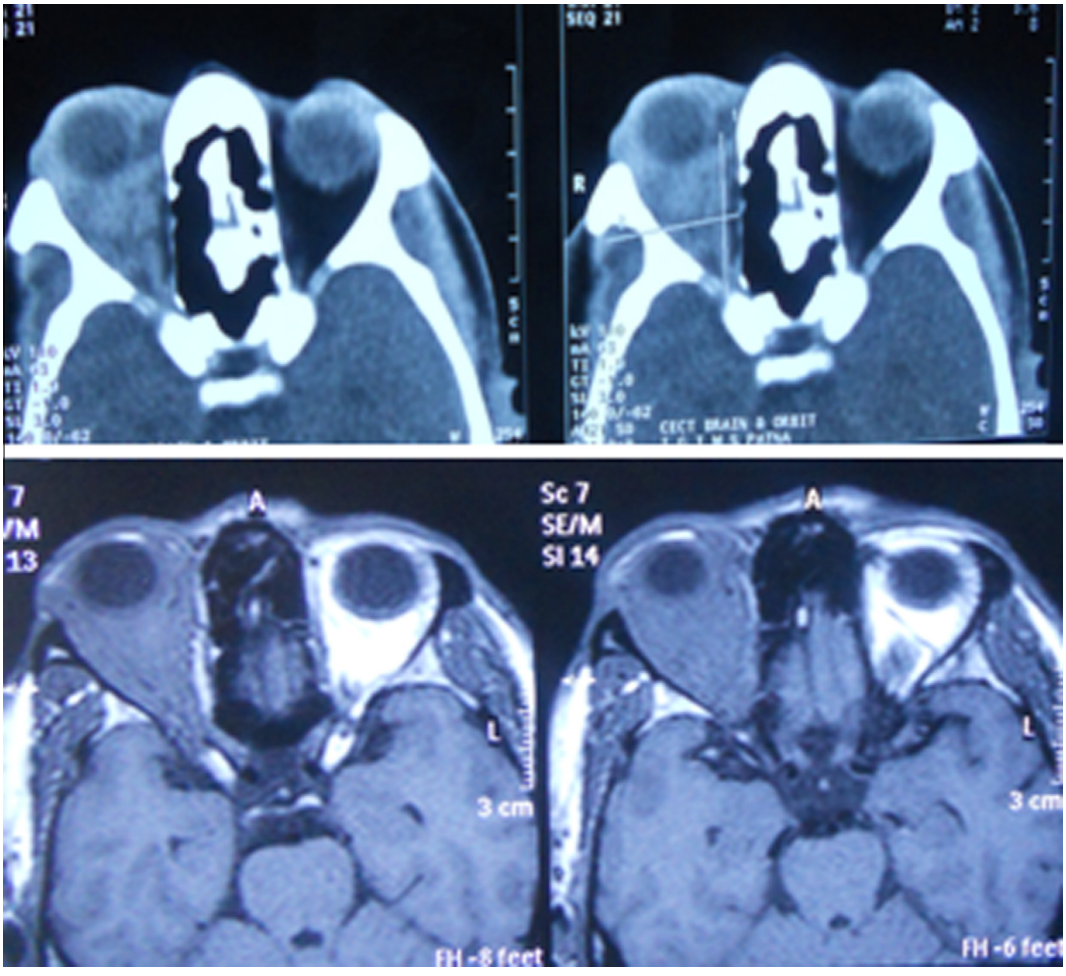

Figure 2 Axial CECT image showing enhancing mass in the intra or extraconal compartment with invasion of extra ocular muscles (upper panel). MRI showing hyper intense mass on T2 weighted images in the conal compartment with a variable extent of involvement of the extra ocular muscle (lower panel) (Fig. 2).

response as documented in post chemotherapy CECT scan. After chemotherapy 6 (26%) patients had a complete remission, 11 (47.8%) patients had a partial response. The post chemotherapy response was not documented for 6 cases.

Radiotherapy

Involved field radiotherapy was used for all patients. Radiation was delivered by 3DCRT technique. The median dose of radiation was 45 Gy (range 20–45 Gy). The radiotherapy course was well tolerated. The commonest toxicity noted was grade I skin reaction noted in approximately all cases. Conjunctivitis grade I was noted in most patients and few had grade II reaction. There was no treatment break because of toxicity. In all planning bolus 5 mm was placed to achieve homogenous dose distribution. The dose to the organ at risk for all plans was noted well below the normal tolerance limit.

Disease control

At a median follow up of 26.8 months (7.5–103.4 months) local disease control was 100% and overall survival was 100%. None of the patients had systemic disease recurrence. However, survival analysis was not performed because of event.

Late toxicity

One patient was found to have keratitis in the involved eye and managed conservatively. One patient developed cataract and underwent cataract surgery.

Discussion

Primary orbital lymphoma is uncommon and accounted for 1% of all NHL [2]. POL is found to arise from the lacrimal gland, conjunctiva, ocular muscles and eyelid predominantly in the 6th decade [7]. In the present series also the incidence is more in the 6th decade and 9 patients were aged 60 years or older. In the literature conflicting reports have been published regarding male or female preponderance. However, our experience is little different and we found POL to be twice more frequent in male. A large majority (more than 75%) of POL has been reported to be with low grade lymphoma and they have an indolent clinical course [5]. Mucosa associated lymphoma (maltoma) is the commonest histologic subtype followed by follicular lymphoma, DLBCL, MZL, etc. On the contrary only 2 patients had maltoma histology in the present series. 10 patients had low grade histology including low grade B cell NHL, maltoma [4]. The remaining 7 had DLBCL and small cell NHL suggesting a different etiology and clinical behavior in the present cohort. Most commonly patients present with palpable orbital mass, followed by ptosis, proptosis and eye irritation. In approximately 20% (10–25%) of cases the involvement has been reported to be bilateral, however all patients in this study population were found to have disease localized to one eye only [8]. *Chlamydia psittaci* DNA has been found in 80% cases of orbital Lymphoma [8]. Efforts have been made to eradicate POL with doxycycline but without substantial success. Hence, the role of antibiotics in the treatment of POL needs further standardization. However, in this cohort antibiotics were not used. Surgery has a limited role in the curative treatment of POL attributed to difficulty to achieve complete surgery. Esik et al. reported 0% local relapse free survival after local surgery alone. Hence, surgery is not considered curative in our institute and is not offered in any of these patients [6].

The role of chemotherapy for POL has been questioned in different series [6,9–11]. In low grade POL chemotherapy has not been reported to confer any survival improvement which may be attributable to the indolent nature of disease [12]. Another hypothesis is that the use of chemotherapy delays the radiation therapy which has long been considered a curative for such cases. The effectiveness of radiation was established when Esik et al. reported 42% local control with chemotherapy in comparison to 100% local control with radiotherapy [6]. However, despite initial good local control 40–67% high grade POL experiences systemic metastasis. Hence, POL with high grade histology merits trial with a combined modality approach. The commonly used chemotherapy regimens COP, CHOP, or RCHOP for nodal NHL have been extrapolated for POL also followed by local involved field radiotherapy [13]. Avelis et al. in a retrospective analysis reported 98% complete response after radiotherapy alone and 100% complete response rate after combined modality therapy [14]. The authors reported 96% and 91% overall survival respectively at 16 years of follow up.

Radiotherapy is considered the primary curative treatment for stage I and stage II POL. In low grade lymphoma radiation alone and in high grade combined modality with chemotherapy may confer long term disease control and overall survival. The evolution of radiation technique has optimized treatment delivery and minimizes radiation toxicity for POL. The 3DCRT and IMRT technique have enabled delivery of radiation more precisely with sparing of OAR [15,16]. In the present series all patients received conformal radiotherapy and completed the planned radiation dose without any grade III or more toxicity. The modern techniques have made radiotherapy more sophisticated limiting the concerns of excessive late toxicity also. However, the optimum radiation dose is often debated and less data are available to comment upon the optimum radiation doses. Authors in different series have advocated a wide dose range (10–57 Gy) [17,18]. However, there is a trend to use a lesser dose of radiation because of concerns of late radiation morbidity. The dose response is quite clear in cases of POL and the local control and the overall survival is poor with a radiation dose of < 30 Gy [17,18]. The literature though discordant shows inclination to accept a radiation dose of 30 Gy after CR and 40 Gy after a PR. We used 45 Gy in conventional fractionation and the compliance was excellent without any serious morbidity. However, the dose was reduced to 36 Gy for low grade histology. Though small, 100% local and systemic control with the combined modality therapy approach should be considered the optimum treatment regimen. The treatment volume is however not very unclear and the entire orbit is considered the target. In a recent review Yadav et al. have clearly shown 33% recurrence in the ipsilateral orbit after partial orbital irradiation [19]. Entire orbit was taken as target for all cases in the present cohort. The excellent local disease control supports the concept of whole orbital radiation only. In the recent years the introduction of conformal radiation in the form of 3DCRT and IMRT has enabled

sophisticated treatment delivery and minimal radiation morbidity. Acute radiation morbidity is often very minimal, particularly after a moderate dose treatment. However, concerns are often expressed about the long term morbidity and cataract remains the commonest late toxicity [5,8]. It has been reported that the incidence of cataract formation is more when the lens is not shielded. The incidence varies from 0–38% with shield and 9–100% without lens shield. At present the conformal radiation enables radiation delivery with a limited dose to lens and other OARs. The improvement in cataract surgery also has made this toxicity easily manageable. Late toxicity like lacrimal gland toxicity, corneal and retinal toxicity is very unlikely in the dose range used in POL. In the present series grade I conjunctival congestion was the most common toxicity noted in all patients. However, there was no treatment interruption. We found no long term toxicity in the series; however the follow up is limited. The study has its limitations owing to the retrospective nature. However, POL is a relatively uncommon disease and it seems difficult to have a proper randomized study. Homogenous radiation target volume delineation and chemotherapy can be considered as strength of the study.

POL is a relatively uncommon entity. The localized nature and low to intermediate grade histology confer long term disease control. A combined modality therapy with a combination of CHOP/COP based chemotherapy and moderate dose of radiotherapy imparts excellent long term local and systemic disease control.

Disclosures

The authors have nothing to disclose.

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Conflicts of interest

The authors have no conflict of interest.

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