Pergamon

Oral Oncol, Eur J Cancer Vol. 32B, No. 6, pp. 420–422, 1996

Printed in Great Britain
0964-1955/96 $15.00 + 0.00

PII: S0964-1955(96)00031-0

Short Communication

Marginal Zone B Cell Lymphoma of the Parotid Glands: Results of a Randomised Trial Comparing Radiotherapy to Combined Therapy

A. Avilés,[1] S. Delgado[2] and J. Huerta-Guzmán[1]

Departments of [1]Hematology and [2]Radiotherapy, Oncology Hospital, National Medical Center, México, D.F. México

39 patients with marginal zone B cell lymphoma (MZBCL) of the parotid glands (stages I or II) were studied. They were randomized to be treated with either radiotherapy alone (extended fields, 4500 cGy) or radiotherapy (the same schedule) plus adjuvant chemotherapy (cyclophosphamide, vincristine and prednisone). The end points were survival and time to treatment failure (TTF). Patients who received radiotherapy alone had a complete remission rate of 100%, the TTF was 90% at 5 years and overall survival at 5 years was 90% with no statistical difference when compared with patients who received combined therapy [100, 80 and 95%, respectively ($P = 0.5$)]. Although adjuvant chemotherapy was well tolerated, the use of this therapeutic approach in patients with early stage MZBCL did not offer any advantage over radiotherapy alone as the initial treatment. Until now, radiotherapy was considered the treatment of choice in this clinical setting of patients. Copyright © 1996 Elsevier Science Ltd

Key words: malignant lymphoma, monocytoid B cell lymphoma, marginal zone B cell lymphoma, radiotherapy, combined therapy

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INTRODUCTION

Monocytoid B cell lymphoma is a well-recognized clinicopathological entity characterised by the presence of monocytoid B cells, which are pale with lucent cytoplasm and often with well-delineated cell borders. The pale cytoplasm surrounds extremely bland-appearing nuclei, which are often ovoid or slightly reniform [1, 2]. Recently, this clinicopathological disease has been allocated to the low-grade malignant lymphoma group as marginal zone B cell lymphoma (MZBCL). This pathological entity has been included in mucosa-associated lymphoid tissue (MALT) as a different form of malignant lymphoma when compared with other low-grade malignant lymphomas because its clinical presentation, immunophenotyping profile and biological course are completely different [3].

Numerous studies have confirmed the neoplastic nature of this variant of lymphoma as well as its B cell nature, based on immunohistochemical and immunogenetic studies [2]. Although MZBCL can be seen in any lymph node, extranodal distribution is different; salivary glands and the lungs are the most frequent extranodal presentation. The involvement of salivary glands, especially in parotid glands, is generally preceded by Sjöegren's syndrome. In this case, neoplastic cells are around the epimyoepithelial islands [4].

Marginal zone B cell lymphoma has been described as a unique anatomic presentation, but in some cases the disease is disseminated. Treatment remains controversial because the natural history of this entity shows that a response would be achieved with a single therapy. However, relapse is the rule and transformation to high-grade malignant lymphoma will be frequent [5–7].

In advanced stages, combined chemotherapy has been observed to achieve complete response (CR), but overall survival has not been reported and comparative regimens are not available [8] because, in some anatomical regions, MZBCL generally is localised or with local spread the use of radiotherapy appears to be the best therapeutic approach [4]. Local control has been reported with adequate treatment, but like low-grade lymphomas, relapse is frequent in

Correspondence to A. Avilés, Apartado Postal 7-1220, 06700, México, D.F., México.
Received 7 Mar. 1996; provisionally accepted 28 Mar. 1996; revised manuscript received 1 May 1996.

unradiated fields. For this reason, combined therapy was considered to avoid the possibility of relapses and increase the possibility of cure.

We began a prospective clinical trial in a small group of patients with MZBCL localised to the parotid glands (stage I) or adjacent lymph nodes (stage II), who were treated with either radiotherapy alone or combined therapy to evaluate the useful and toxicities of the latter therapeutic approach.

MATERIALS AND METHODS

Between May 1989 and December 1993, patients with confirmed diagnosis of MZBCL on H/E and immunohistochemical methods were considered as candidates for the study. Diagnosis criteria were as described previously [1, 3]. Immunophenotyping showed Pan B +, CD 5 −, CD 10 −, CD 23 −, CD 43− (has been reported positive in some studies [3]) and sIgM +.

Criteria for entry to the study were as follows: diagnosis of MZBCL confined to the parotid glands, clinicopathological stage I (localised) or with local involvement of adjacent lymph nodes (stage II), previously untreated unless by corticosteroids if the patient had a previous diagnosis of Sjöegren syndrome, age >18 years old with no upper limit, normal renal, hepatic and cardiac functions, immunodeficiency virus test negative, no pregnancy.

Patients underwent the following tests: complete blood count with differential and platelet count, serum chemistry panel, urinalysis, serum lactic dehydrogenase and beta$_2$ microglobulin levels, chest-X ray, and a computerised tomography scan of thorax, abdomen and pelvis. They also had barium studies and upper digestive endoscopy with gastric biopsies, bone marrow smear and trephine, and serological determination for human immunodeficiency virus.

If the patients fulfilled these criteria they were randomised to received either: (a) radiotherapy: irradiation administered with a 6 MeV linear accelerator at the rate of 750–1250 cGy per week with a total of 4500 cGy. The areas clinically involved, the locoregional nodal region and Waldeyer's ring were included in the fields of radiation; (b) radiotherapy at the same dose and schedule as in (a). Four weeks after the irradiation was completed, the patient began adjuvant chemotherapy with cyclophosphamide, 800 mg/m^2 i.v., on day 1, vincristine 1.4 mg/m^2 i.v., on day 1 (maximum doses 2 mg) and prednisone 50 mg/m^2 p.o., daily, for days 1–5. Each cycle was administered every 21 days to complete six cycles. No further treatment was given.

Complete response was defined as the disappearance of all clinical evidence of disease for at least 6 months. Partial response was defined as the reduction of >50% on tumour mass for at least 6 months. Failure was defined as when the patient had a reduction of <50%, or the presence of new lesions. Time to treatment failure (TTF) was defined from when the patient achieved CR until the first evidence of relapse. Survival was considered as from when the patient began treatment to death secondary to tumour progression or secondary to treatment. Survival and TTF were calculated by the Kaplan–Meier method [9]. Differences between groups were analysed using the generalised Wilcoxon's test of Gehan.

Table 1. Patients' characteristics

	Radiotherapy	Combined therapy
Number	19	20
Sex		
Male	7	5
Female	12	15
Age (years)		
Median	61	64
Range	39–80	45–76
Stage I	14	12
Stage II	5	8
Clinical risk		
Low	13	14
Low–intermediate	6	8

RESULTS

45 cases were diagnosed as MZBCL. 6 patients refused treatment and were not considered to enter the study. The demographic characteristics of the 39 evaluable patients can be seen in Table 1. No differences were observed between the two groups. Complete response was achieved in all cases. After a median follow-up of 45 months, six relapses have been observed: two in the radiotherapy group and four in the combined therapy group. Figure 1 shows the actuarial TTF, median not yet reached in both groups; 90% of the patients treated with radiotherapy alone remained in the first CR compared with 80% of the patients who were treated with combined therapy ($P = 0.5$). 3 patients died. The 2 patients who relapsed in the radiotherapy group died, 1 secondary to tumour progression and one to myelosuppression secondary to aggressive chemotherapy. 1 patient in the combined group relapsed and died secondary to tumour progression. Figure 2 shows the actuarial overall survival. Again, no differences were observed between the two groups ($P = 0.5$).

Toxicity

Radiotherapy was well tolerated. 10 patients had transitory mucositis. Chemotherapy was also well tolerated, no infections related to treatment were observed and granulocytopenia grade I was observed in 3 patients; no delays on treatment were observed. The dose intensities for cyclophosphamide and vincristine were 0.95 and 0.93, respectively. With a median follow-up of 45 months (range 36–88

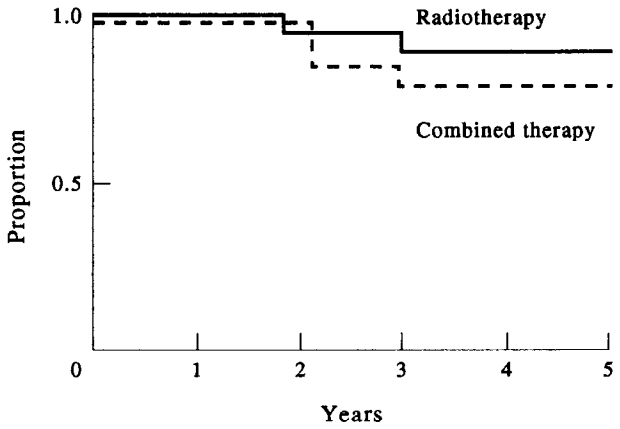

Fig. 1. Actuarial duration of time to treatment failure.

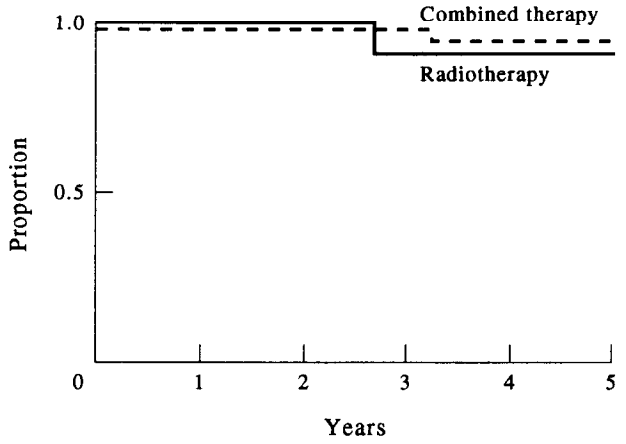

Fig. 2. Overall survival.

months), no late side-effects, such as acute leukaemia or secondary tumours, have been observed.

DISCUSSION

The so-called monocytoid B cell lymphoma was first proposed by Sheibani *et al.* [2] to describe a different form of malignant lymphoma with special pathological features and unusual clinical outcome, similar to low-grade lymphoma. Numerous studies have confirmed the neoplastic characteristics of these lesions, because atypical monocytes can be confused with neoplastic B cells. As mentioned previously, MZBCL has been proposed to replace monocytoid B cell lymphoma, in the same group of MALT lymphoma. Although both variants of lymphoid malignancies have been considered closely, clinical presentation and management are different [8, 10].

Numerous overlapping morphological and immunophenotypical features suggested closely related lymphomas; also they have microanatomic and distribution differences reflecting the fact that the extranodal MALT lymphoma is mucosa-based and the MZBCL is node-based [11, 12].

Marginal zone B cell lymphomas have better outcomes than MALT lymphomas. The latter patients have a more aggressive course and treatment will be different [11].

In patients with MZBCL, treatment remains to be determined. Radiotherapy has been used in some patients with stage I with local control, but the number of patients were small and curiously long-term follow-up is not available [4, 6], thus, definitive conclusions cannot be drawn. The biological course of MZBCL resembles the course of low-grade malignant lymphomas. For this reason, relapses in anatomic sites previously not irradiated has been the rule [7]. The use of cytotoxic drugs as single or combined chemotherapy has been advocated in disseminated disease [8], but in the early stages, no reports are available.

The possibility that early stages treated with radiotherapy can relapse offer the opportunity to treat these types of patients with combined therapy, like low-grade malignant lymphoma, in an attempt to avoid the possibility of relapse and improve the duration of remission and cure [13]. However, the risk of using cytotoxic drugs as alkylators has been associated with late side-effects such as the presence of acute leukaemia and secondary tumours, which can eliminate the possible benefits of this therapeutic approach.

Our results in a small group of patients with localised MZBCL in parotid glands (the most frequent extranodal presentation) shows that radiotherapy alone is sufficient to control local disease and, in truly early stages, relapse is a rare event. The use of adjuvant chemotherapy did not improve TTF and overall survival.

Nevertheless, the treatment was well tolerated and late side-effects were not evident. Marginal zone B cell lymphoma remains a rare clinicopathological presentation of malignant lymphoma, less than 5% of patients can be diagnosed as MZBCL even in reference centres such as our institution; for this reason, the number of patients is small, but taken into consideration the results of the study was closed.

We feel that radiotherapy remains the best therapeutic option in the treatment of early stage MZBCL. The use of adjuvant chemotherapy in the above-mentioned schedule is not useful because it did not improve TTF and overall survival.

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