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# Combined Therapy for Angioimmunoproliferative Lesions

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**43 patients with a diagnosis of angioimmunoproliferative lesions (AIL) entered onto a prospective clinical trial to evaluate the use of combined therapy as a primary therapeutic approach. Patients were treated initially with involved field radiotherapy 40–55 Gy (40 patients received 45 Gy) followed by six cycles of chemotherapy which consisted of CEOP-Bleo (cyclophosphamide, epirubin, vincristine, prednisone and bleomycin). Complete response was achieved in 41 cases (95%). At a median follow-up of 40 months, 40 patients (91%) remain in first complete remission. 2 patients died during radiotherapy secondary to sepsis and tumour progression. Treatment was well tolerated. The treatment of AIL remains controversial. Our results show that combined therapy appears to be the best therapeutic approach in patients with this type of malignant lymphoma. More studies are necessary to define the role of combined therapy in patients with AIL.**
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## INTRODUCTION

ONLY RECENTLY have angioimmunoproliferative lesions (AIL) been recognised as a distinctive biological and clinical entity in the spectrum of malignant lymphoma [1–5].

The clinical syndrome is identified by unremitting slowly progressive ulceration and necrosis of the nose, paranasal sinuses and hard palate, commonly with destruction of soft tissues and bone. The patients has been previously referred to as lethal midline granuloma or polymorphic reticulosis. Although diagnosis can be difficult because of the presence of inflammatory cells and necrosis, clonality and aggressive clinical course has identified these cases as malignant lymphoma. In most cases, immunophenotype showed T cell characteristics [5–8].

However, the best treatment remains unclear in these patients. Radiotherapy has been used with excellent local tumour control but the rate of systemic recurrence is high, generally in lungs, bone marrow or liver [4, 5, 9, 10]. If chemotherapy is the first therapeutic approach, infection and local bleeding are common [11, 12].

For this reason, we began a prospective clinical trial to define if the use of involved field radiotherapy followed by systemic chemotherapy could improve the duration of remission and survival in these patients. The results achieved with this therapeutic approach will be presented herein.

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## PATIENTS AND METHODS

Patients with a diagnosis of AIL were included in the present study. Pathological and immunophenotyping criteria have been reported previously [5]. Only patients with disease localised to the centrofacial anatomical region were considered as candidates for the study. Criteria entry were as follows: age 18–65 years, localised disease, no prior treatment, negative test for acquired immunodeficiency syndrome, performance status $\geqslant 70\%$ according to Karnofsky's criteria, intermediate or high risk according to our clinical risk classification [10] and cardiac function measured by left ventricular ejection fraction (LVEF) $\geqslant 50\%$.

Evaluation included a thorough history and clinical examination, complete blood counts, liver and renal function tests, serum determinations of lactic dehydrogenase (LDH), uric acid, protein electrophoresis, beta-2-microglobulin and urinalysis. Chest X-ray, computerised tomography (CT) of the abdomen, pelvis and paranasal sinuses, barium studies and upper endoscopy with gastric biopsies were also performed. A bone marrow biopsy and aspirate were carried out in each patient.

All patients were treated with megavoltage irradiation ($^{60}$Co or 6 mV linear accelerator). The patients received involved field treatment with daily fractions of 1.8–2.0 Gy during 4–6 weeks. Total doses ranged between 40 and 55 Gy, but most patients (40 cases) received 45 Gy. No prophylaxis was given to the central nervous system even in the presence of bone destruction. Four weeks after completion of radiotherapy, the patients entered systemic chemotherapy treatment which consisted of six cycles of CEOP-Bleo [cyclophosphamide 600 mg/m$^2$, intravenous (iv), day 1; epirubicin 70 mg/m$^2$, iv, day 1; vincristine 1.4 mg/m$^2$, iv, day 1; prednisone 60 mg/m$^2$, orally, days 1–5 and bleomycin 10 mg/m$^2$, iv, day 14]

*Table 1. Clinical and laboratory characteristics*

| | No. | % |
|---|---|---|
| Number of cases | 43 | 100 |
| Median age (years) | 47 | |
| Sex: Male | 27 | 62 |
| Female | 16 | 37 |
| B symptoms | 36 | 83 |
| Lactic dehydrogenase (>275 U/l) | 35 | 81 |
| β-2-microglobulin (>3.5 ug/ml) | 30 | 69 |
| Histology: Diffuse large cell | 39 | 90 |
| Immunoblastic | 4 | 10 |

administered every 21 days. If haematological toxicity was observed (granulocyte level $< 1.5 \times 10^9$/l and or platelets level $< 100 \times 10^9$/l), treatment was delayed until haematological recovery. When the patient completed the treatment, careful restaging was performed, including CT of paranasal sinuses. If suspicious lesions were observed, surgery (generally Caldwell–Luc) was performed to achieve adequate pathological material.

Complete response was defined as the disappearance of all evidence of tumour for at least 6 months. If tumour remained after treatment the patient was considered a failure. No partial remission was considered in our study. Relapse-free disease (RFD) was considered as the time from the patient achieving complete response to the first clinical, radiographic and pathological confirmation of relapse. Survival was considered from diagnosis until death of the patient either due to tumour progression or due to treatment. Kaplan–Meier actuarial curves were carried out to analyse both RFD and survival [14] and compared using the Wilcoxon's Gehan method [15]. Cox's method was performed to evaluate the value of prognostic factors on duration of RFD and survival [16].

## RESULTS

Between July 1987 and December 1991, 43 patients were entered in to the study. Clinical and laboratory characteristics can be seen in Table 1. As in to previous reports, most patients had adverse prognostic factors such as B symptoms, and elevation of LDH and β-2-microglobulin [5].

2 patients died during radiation therapy from sepsis and tumour progression. 41 patients (95%) achieved complete remission after completion of combined therapy. With a median follow-up of 40 months, only 1 patient had relapse, 14 months after completion of treatment. She relapsed in the lungs and liver, no response was achieved with salvage chemotherapy and she died due to tumour progression.

Figure 1 shows the RFD for all patients. Figure 2 shows the overall survival, in both cases median had not been reached. At 5 years, 91% of the patients remain alive and free of disease.

*Toxicity*

11 cases had moderate mucositis during radiation treatment. 4 cases developed local infection, 2 were controlled with appropriate antibiotics, but lymphoma was seen in remission. 2 patients developed infection and tumour progression and both cases died from septicaemia. During chemotherapy, 22 patients developed granulocytopenia level 3 ($< 1.0 \times 10^9$/l), with seven infectious episodes; all cases resolved well with treatment. Paresthesias were present in 7 patients and nausea/vomiting was observed in 13 cases. LVEF taken after chemotherapy was normal in all cases.

Prognostic factors lost potential importance with the use of combined therapy. Multivariate analysis showed that none of the prognostic factors evaluated: age, sex, histology, bone destruction, levels of LDH and β-2-microglobulin influenced the RFD and overall survival (data not shown).

## DISCUSSION

The management of AIL remains controversial; this may in part be related to the diversity of how patients are initially evaluated. Deficiency of histological evaluation or inadequate biopsies in patients with inflammation and necrosis are common causes of inadequate diagnosis. Recently, Grange *et al.* described a clinical, radiological and pathological assay designed to diagnose AIL more easily [4]. Also, immunophenotyping studies confirm the T-cell spectrum in most cases with angiocentric lesions [17]. Lipford *et al.* showed that the angioproliferative pattern has a worse prognosis compared to patients without this pathological finding [6]. This finding has been confirmed in a previous study in our institution [5].

Treatment remains unsatisfactory. Radiotherapy can achieve excellent local control, but the spread of malignant cells produces relapses in other anatomic sites [12, 18]. On the other hand, when chemotherapy is the first choice, sepsis and local bleeding are common with lethal complications in most patients [12].

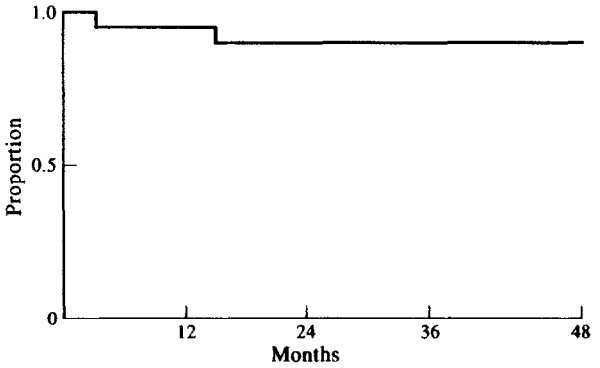


**Fig. 1. Actuarial curve of relapse-free disease in patients with angioimmunoproliferative lesions treated with combined therapy.**

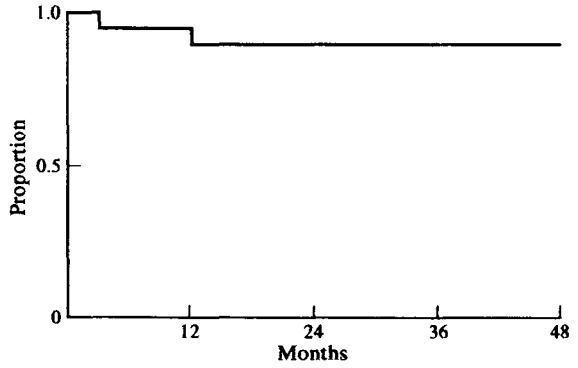


**Fig. 2. Actuarial curve of survival.**

Combined therapy has been useful in patients with localised aggressive lymphoma [19–21]. For this reason, we began the present study to evaluate if the use of radiotherapy followed by conventional chemotherapy can improve duration of RFD and survival in patients with AIL. Our results show that patients treated in this fashion can achieve good local control with initial radiotherapy and the possibility of relapse can be controlled with the use of chemotherapy. The toxicity was mild and the patients who died during treatment had tumour progression and infectious episodes; with normal values of leucocytes and granulocytes the use of antibiotics prophylaxis can probably be useful in some selected cases. Our results show that the use of combined therapy is presently the best therapeutic approach in patients with AIL, with 91% alive and free of disease at 5 years. We believe that in the past there has been a tendency to treat patients half-heartedly and for this reason long survival has been observed in few patients. Aggressive treatment may be considered in all patients with AIL; we demonstrate that the use of combined therapy is the best therapeutic approach and we hope that our results encourage others to treat these patients with combined therapy.


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