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Original Paper

Anaplastic Large Cell Lymphoma (CD30+/ Ki-1+). Analysis of 35 Cases Followed at GISL Centres

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Between January 1988 and June 1992, 35 patients with primary anaplastic large cell lymphoma (ALCL)CD30+ were referred to one of the institutions participating in GISL (Gruppo Italiano per lo Studio dei Linformi). 16 patients were treated with ProMACE-CytaBOM, two with MACOP-B, one with CHOP and one with LSA_2-L_2. As of November 1990, all newly diagnosed patients were treated with MOPP/EBV/CAD hybrid. 27 (77%) cases of ALCL CD30+ and 8 (23%) cases of Hodgkin's-related (HR) lymphoma CD30+ were diagnosed. Extranodal disease was present in 22 cases (63%), and 8 patients (23%) had primary bone marrow involvement. Twenty-three complete remissions (CR) (66%), six partial remissions (PR) (17%) and six no remissions (NR) (17%) were achieved with induction therapy. Results achieved with ProMACE-CytaBOM and MOPP/EBV/CAD hybrid were comparable. The overall response rate (CR+PR) was 85% for patients with classic ALCL CD30+ and 87% for those with HR lymphoma CD30+. The 3 year estimated overall survival rate was 66% and the 3 year relapse free survival rate was 65% for the entire group. The only significant favourable prognostic factor was the achievement of CR with initial therapy. Our findings suggest that ALCL (CD30+/Ki-1+) has a clinical outcome similar to aggressive non-Hodgkin's lymphoma (NHL). The use of an anthracycline-containing regimen will provide a change of cure in approximately 65% of cases.

Key words: anaplastic large cell lymphoma (CD30+/Ki-1+), CD30+ Hodgkin's-related lymphoma, non-Hodgkin's lymphoma, aggressive chemotherapy
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INTRODUCTION

ANAPLASTIC LARGE CELL lymphoma (ALCL) CD30+/Ki-1+ represents a new distinct pathological entity [1], and in the updated Kiel classification it has been included in the group of high grade, non-Hodgkin's lymphomas (NHL) [2]. The disease is characterised by a prominent paracortical involvement of the lymph nodes, with areas of necrosis and intrasinusoidal dissemination. Large cells with pleomorphic nuclei, one or more nucleoli and abundant vacuolated cytoplasm are easily detectable [3]. The ALCL CD30+ cells express the lymphocyte activation antigens CD30, CD25, CD71 and Ia. In the majority of cases, the neoplastic cells are T-cell derived, with a smaller number of cases originating from B or null cells [4]. In addition to the classic ALCL CD30+, a Hodgkin's-related (HR) variant has also been recognised. This form was originally included in the syncitial variant of nodular sclerosis or in the lymphocyte depletion subtype, and is morphologically almost indistinguishable from ALCL. However, the anaplastic cells in the Hodgkin's disease variant are CD15+, LCA− and EMA−; while classic ALCL CD30+ cells are CD15−, LCA+ and EMA+ [5]. Approximately one-third of ALCL has a chromosomal translocation t(2;5)(p23;q35). This rearrangement involves a nucleolar phosphoprotein gene (*NPM*) on chromosome 5 and a protein tyrosine kinase gene (*ALK*) on chromosome 2 [6].

Patients with ALCL CD30+ usually present an involvement of extranodal sites, such as skin, lung, gastrointestinal tract, soft tissue and bone marrow. Despite the increasing interest in the disease, response to therapy and prognosis of ALCL CD30+ are largely unknown. Most of the published studies were performed on cases in which ALCL CD30+ was diagnosed retrospectively,

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and with patients observed over a wide period of time and treated with different approaches.

In order to investigate the effectiveness of available therapeutic approaches, the Italian Lymphoma Study Group (Gruppo Italiano per lo Studio dei Linformi, GISL), in 1988, prospectively defined the guidelines for the treatment of patients with ALCL. In this report, we present the results of strategies adopted in 35 consecutive patients.

PATIENTS AND METHODS

Between January 1988 and June 1992, 39 patients with primary ALCL CD30+ were referred to one of the institutions participating in GISL. For 4 patients, there was insufficient clinical data and they were excluded from the present report.

The diagnosis of ALCL was performed according to standard diagnostic criteria, including classic histopathological features [3] and reactivity of tumour cells with CD30 or Ber-H2. Diagnosis was made on lymph node samples in 27 cases and on bone marrow biopsies in 8 cases.

Immunophenotypic analysis was performed on frozen or paraffin-embedded sections by avidin–biotin–peroxidase complex. To detect CD30, we used Ki-1 antibody (Dako Corp.) on frozen sections and Ber-H2 (Dako Corp.) on paraffin-embedded sections. Specificity of immunoreactions was evaluated by using known positive and negative tissue sections as controls. Other monoclonal antibodies used included: CD2, 3, 4, 5, 8, 45 RO (T-cells); CD19, 20, 22, anti-IgM (B-cells); CD15 (Reed Sternberg cells, Hodgkin's cells, monocytes, myeloid cells); anti-epithelial membrane antigen (epithelial cells, plasma cells, non-Hodgkin's); LCA (leucocytes); anti-keratin (epithelial cells); S-100 (melanocytes). We could not always use all these antibodies in every patient, generally due to insufficient material. ALCL were interpreted as being CD30+ if at least 75% of neoplastic cells stained for the CD30 antigen. A lymphoma was determined to be of B-cell lineage when positive staining for one or more pan-B antibodies was present in the absence of positive staining for pan-T antibodies. A lymphoma was determined to be of T-cell lineage upon demonstration of positive staining for one or more pan-T antibodies in the absence of positive staining for pan-B antibodies. A lymphoma was determined to be null when no staining was demonstrable after testing for at least two pan-T and two pan-B antibodies. A lymphoma was considered to be of undetermined lineage when staining was negative for both B and T cell antibodies, but less than two were tested for either or both cell lineages. In 3 cases, a cytogenetic analysis was also performed. 8 patients were classified as affected by CD30+ HR lymphoma, on the basis of a layer of monomorphic Sternberg-like cells, the presence of several mitotic figures, residual aspects of nodular sclerosis, and CD30 positivity. All patients underwent clinical staging according to the Ann Arbor system. Staging procedures included a full history and physical examination, blood cell and differential counts, liver function tests, serum creatinine and LDH (lactate dehydrogenase) assessment, bone marrow biopsy, chest X-ray, chest, abdomen and pelvic computer assisted tomographic (CAT) scan, and human immunodeficiency virus antibody screening.

Treatment

Until October 1990, patients with ALCL CD30+ were treated with the regimens adopted by GISL for high grade NHL. 18 of 20 patients were enrolled in prospective studies, 16 cases being treated with prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue (ProMACE-CytaBOM) [7], and two with methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) [8]. The remaining 2 patients were ineligible for these controlled studies; thus, one received cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) [9] and the other was treated with a regimen used to treat acute leukaemia (LSA_2-L_2) [10]. In all regimens, doxorubicin was replaced by a 20% higher dose of epidoxorubicin. As of November 1990, all newly diagnosed patients were treated with mecloretamine (substituted in alternate cycles by CCNU), vindesine, melphalan, prednisone, followed on day 8 by epidoxorubicin, vincristine, and procarbazine, and on day 15 by vinblastine and bleomycin (MOPP/EBV/CAD hybrid) [11]. This very aggressive regimen was originally designed for patients with unfavourable, advanced Hodgkin's disease, and was subsequently adopted by the GISL for patients with ALCL CD30+. After chemotherapy, 6 patients received radiotherapy (RT) on the site of previous bulky disease. One patient achieved complete remission with six courses of ProMACE-CytaBOM plus 40 Gy of RT on mediastinal field, and subsequently underwent successful autologous bone marrow transplantation.

Assessment of response

Complete remission (CR) was defined as the disappearance of all clinical evidence of the disease and the normalisation of all laboratory values and radiographs that were abnormal before therapy. CR was assessed 1 month after the end of therapy. Therefore, patients who achieved CR during therapy, but relapsed within 30 days of suspension were classified as having no response. Partial remission (PR) was defined as a greater than 50% reduction in the largest dimension of each site of measurable disease for at least 1 month. No remission (NR) was defined as less than 50% regression or stable or progressive disease.

Statistical methods

All data were analysed with the Statistical Package for Social Science (SPSS) [12]. Survival was measured from the date of diagnosis to the date of the last observation or death. Disease-free survival (DFS) was calculated from the onset of CR to the first evidence of relapse. Survival and DFS curves were estimated by the life-table method. The log-rank test was used to assess the significance of differences between groups [13].

RESULTS

The clinical features of the 35 patients with ALCL CD30+ are summarised in Table 1. 14 patients (40%) presented with bulky disease, primarily involving the mediastinal site (12 patients). A mediastinal bulky mass was observed in 22% of patients with classic ALCL CD30+ and in 75% of patients with HR-ALCL CD30+. The bulky lesions ranged from 7 to 16 cm, with a mean value of 8.5 cm. Three additional patients (9%) had measurable lesions greater than 3 cm in diameter. Extranodal disease occurred in 22 cases (63%). 8 patients (23%) had primary bone marrow involvement (7 cases in common ALCL and 1 case in HR-ALCL), and in 5 patients (14%) the disease spread to the lung. In 6 of the 8 patients with bone marrow involvement markers of lineage (T in 4 cases, B in 1 case, undetermined in 1 case) were detected. Constitutional symptoms were present in 21 (60%) cases. 27 (77%) cases of ALCL CD30+ and 8 (23%) of CD30+ HR lymphoma were diagnosed.

The B- and T-cell phenotypes of the lymphomas of 26 patients were examined. Nine lymphomas (35%) showed a T-

Table 1. Patient characteristics

No. of patients	35
Mean age (years)	40
Range	14–74
Sex	
Male	18
Female	17
Performance status (ECOG)	
0–1	27
2–3	8
Stage	
I	3
II	8
III	8
IV	16
Bulky disease	
Present	14
Absent	21
Systemic symptoms	
Present	21
Absent	14
Extranodal sites	
Waldeyer	1
Spleen	2
Bone marrow	8
Liver	3
Lung	5
Stomach	3
Breast	2
Treatment	
ProMACE-CytaBOM	16
MOPP/EBV/CAD hybrid	15
Other	4

cell phenotype and 10 (38%) a B-cell phenotype, while seven lymphomas (27%) were considered to be of undetermined lineage. Only in 2 patients with HR-ALCL was the cell lineage detected, with one a case of B and the other of T cell HR-ALCL. We also studied the phenotype of lymphomas from 6 of 12 patients with mediastinal bulky disease (in 5 patients with classic ALCL and in one case of HR-ALCL); the only HR-ALCL studied was considered to be of T cell lineage; three of five classic ALCL were considered to be of T lineage, one of B lineage and the last one was considered to be of undetermined lineage.

A cytogenetic analysis was performed on lymphamatous nodes of 3 patients, but none of these cases showed the typical translocation t(2p23;5q35). All 35 patients were assessable for response. Twenty-three CR (66%), six PR (17%), and six NR (17%) were achieved with induction therapy. The overall response rate (CR+PR) was 85% for patients with classic ALCL CD30+ and 87% for those with HR lymphoma CD30+.

16 patients were treated with ProMACE-CytaBOM. In 3 cases, this was followed by involved field radiotherapy (RT). 10 patients (62.5%) achieved CR, 2 (12.5%) PR, and 4 cases failed to respond (25%). One patient relapsed 3 months after the end of induction therapy and died of disease progression 3 months later. One patient relapsed after 12 months and achieved a second CR with six cycles of MOPP. At the last follow-up, 9–60 months after initiation of therapy, 9 patients (56%) remained disease-free.

Both patients treated with MACOP-B achieved CR. One patient had an early relapse and died 9 months after diagnosis. The other patient is still in CR after 57 months. The patient treated with CHOP achieved a CR and was well and free of disease 15 months later. Finally, one patient with Stage 2 B bulky disease was treated with the LSA_2-L_2 protocol. She failed to obtain a remission and died 3 months after diagnosis.

From November 1990, all patients affected by ALCL CD30+ were treated with the MOPP/EBV/CAD hybrid regimen, according to the GISL guidelines. In the group of 15 patients enrolled in this prospective trial, 10 CR (67%) and 4 PR (27%) were achieved. In 3 cases, chemotherapy was followed by involved field RT. After a median follow-up of 19 months, no relapses were recorded in the group of patients who obtained CR. 2 of the 5 cases failing to achieve CR, are alive with active disease, and 3 died of disease progression 7, 12 and 13 months after diagnosis.

The 3 year estimated overall survival rate was 66% (Figure 1) and the 3 year relapse-free survival rate 65% for the entire group. Patients treated with ProMACE-CytaBOM have a 4 year survival rate of 65%. Those treated with MOPP/EBV/CAD hybrid have a shorter follow-up, but the 2 year survival rate is 75%. Comparing the survival curves for the first 2 years of follow-up, no differences emerged between the groups ($P = 0.94$). Patients were evaluated for several possible prognostic factors, including sex, performance status, advanced stage, systemmmic symptoms, bulky disease, bone marrow involvement, low haemoglobin and high LDH levels. At 3 years, the survival curves were similar in all subgroups. In the present series, the outcome of patients with bone marrow involvement was surprisingly favourable. Moreover, no differences in survival rates were found in patients with two or more adverse prognostic factors as compared to those presenting only one or none. The only significant prognostic factor was the response to initial therapy. As expected, patients achieving CR experienced a better outcome than those in PR or NR at the end of induction therapy (89% versus 38%, $P = 0.002$).

DISCUSSION

ALCL is a relatively uncommon disease. The 39 cases of ALCL identified in the GISL Registry (the registry records all new cases of malignant lymphoma referred since 1988 to centres participating in GISL) represent 2.7% of all cases of NHL. In other studies, the incidence of ALCL ranges between 2 and 7% [4, 14]. In recent years, ALCL has emerged as a distinct clinicopathological entity, primarily of interest to pathologists [5]. Many reports have been published describing the morphological and immunophenotypic characteristics of ALCL CD30+

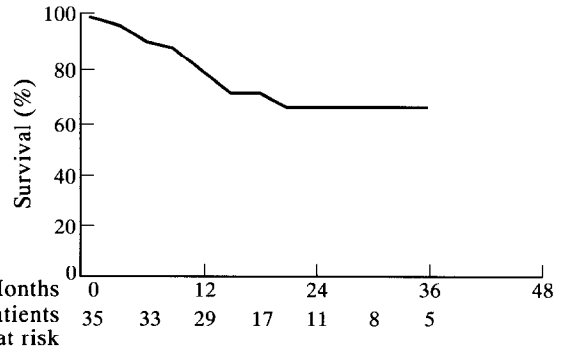

Figure 1. Three-year overall survival of 35 patients with primary CD30+ anaplastic large cell lymphoma followed at GISL centres.

in detail. Moreover, the main emphasis has been placed on distinguishing the classic ALCL CD30+ from the HR lymphoma CD30+, and differentiating primary and secondary ALCL CD30+.

The clinical and epidemiological characteristics of our patients differ in some aspects from other reports. The disease has been described as affecting men more frequently than women, and frequent cutaneous involvement has also been reported. However, in our series, the disease showed no male predominance, rates being comparable for men and women. Patients with cutaneous ALCL CD30+ are usually reported as having a relatively good prognosis, and sometimes these patients are cured by dermatologists. None of our patients presented cutaneous lesions: we did, however, record a significant (23%) incidence of bone marrow involvement, in agreement with Chott and associates [15] who observed bone marow involvement in 7 of 23 cases (30%). Many studies provide no information on the frequency of bulky disease. Only Shulman and colleagues [16] have investigated this aspect, reporting bulky disease in 25% of cases. We found bulky lesions in 40% of patients, primarily in the mediastinal site.

Useful data on the course of the disease and its responsiveness to current therapies are also limited. The effect of treatment on survival is difficult to determine because, in the majority of reports, few details are given on the delivered therapy. Moreover, most studies have been performed on series of patients observed over a long, and in some cases, unspecified period of time. Chan and associates [14] have described 16 cases of ALCL CD30+ treated with different therapeutic approaches. 3 patients presenting only cutaneous involvement had no further treatment except excision and were alive after 1–3 years. 2 patients with cutaneous and extracutaneous disease were treated with combination chemotherapy. Both achieved CR lasting 12 and 30 months. Patients with visceral, non-cutaneous disease had a poor prognosis with conventional chemotherapy: only 4 of 11 patients were alive after a short follow-up [14]. In a series of 24 patients treated with different chemotherapy regimens, Penny and colleagues [17] reported eight CR (33%) and six PR (21%). Most patients had a secondary ALCL CD30+ which developed after *mycosis fungoides*, Crohn's disease, or NHL. Clinically more useful information was provided in Chott's study, in which overall median survival in 41 patients was 13 months [15]. 23 patients received multidrug chemotherapy (most frequently CHOP), 7 chemotherapy plus additional radiotherapy and 4 radiotherapy alone, while 2 patients underwent successful autologous bone marrow transplantation. 5 patients died before starting therapy. A better outcome was observed in patients younger than 40 years, and in patients with stage I or II disease.

An estimated 5 year survival rate of 52% was reported by Nakamura and associates [4] in a series of 30 patients, most of whom were treated with CHOP; Greer and colleagues [18] calculated a 3 year survival rate of 61% in a group of patients treated with a broad spectrum of therapeutic approaches. In a retrospective analysis recently published by Shulman and associates, a 2 year survival rate of 72% was reported in a group of 31 patients treated heterogeneously over time [16]. Finally, other authors have reported their experience in treating limited cases [19, 20]. More recently, Pileri and colleagues have published a study of 69 cases of ALCL CD30+ treated with F-MACHOP and MACOP-B showing no significant differences between the two protocols, with a median follow-up of 54 months, and an overall survival rate of 66% was reported with no differences between common ALCL and HR-ALCL [21].

We studied a group of patients affected by primary ALCL, who were treated homogeneously with combination chemotherapy. 31 patients (89%) were treated with ProMACE-CytaBOM or MOPP/EBV/CAD hybrid, on the objective basis of treatment strategies adopted by GISL. For these reasons, we consider the 66% CR rate and the 61% 3 year expected survival rate as the currently achievable standard results with aggressive chemotherapy. In our experience, ProMACE-CytaBOM and the MOPP/EBV/CAD hybrid are both effective treatments for this disease, but our results are probably not superior to those achieved with CHOP by Chott and colleagues [18] and Nakamura and associates [4]. As regards the neoplastic cells in ALCL CD30+ originating from a T- or B-cell, in 1988 we decided to use the same regimens as adopted in aggressive NHL and for patients with ALCL. However, on the basis of the encouraging results achieved with the MOPP/EBV/CAD hybrid in the treatment of unfavourable, advanced Hodgkin's disease (92% CR in the first 80 available cases) [11], we adopted this regimen for patients with ALCL CD30+. Unfortunately, the results obtained in the first 15 available patients were poorer than expected, suggesting that ALCL CD30+ has a clinical outcome similar to aggressive NHL and not to Hodgkin's disease. Our findings support the committee's decision to update Kiel classification and consider ALCL CD30+ in the group of high grade NHL [2].

Probably owing to the small number of patients, our attempts to define factors of prognostic value failed. Patients with ALCL CD30+ at different stages, with or without systemic symptoms and in the presence or absence of bulky disease or bone marrow involvement, cases with T- or B-cell phenotype, and those with normal or high LDH levels all experienced similar survival rates. The achievement of CR was the only but obviously significant prognostic factor found in our series.

In conclusion, our findings suggest that ALCL (CD30+/Ki-1+) has a clinical outcome similar to aggressive NHL. Currently, the use of an anthracycline-containing regimen will provide a chance of a cure in approximately 65% of cases. However, given the importance of obtaining a complete remission with induction therapy, this uncommon disease also demands efforts to increase the proportion of patients responding to initial therapy. In future, innovative approaches, such as the use of high dose chemotherapy followed by autologous stem cell transplantation, or immunotherapy with immunotoxin containing an anti-CD30 monoclonal antibody and saporin [22] could be used successfully to improve the prognosis of this uncommon disease.

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