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Clinical characteristics, treatment outcome and survival of 36 adult patients with primary anaplastic large cell lymphoma

GIUSEPPE LONGO, CLAUDIA FIORANI, STEFANO SACCHI, VINCENZO CALLEA,* MARCO LOMBARDO,° MASSIMO FEDERICO, CATERINA STELITANO,* FRANCESCO ANGRILLI,° DANIELE VALLISA,§ PAOLO G. GOBBI,@ FIORELLA ILARIUCCI,# ANTONIO FRASSOLDATI, MARIO PETRINI,^ VITTORIO SILINGARDI
FOR THE GRUPPO ITALIANO PER LO STUDIO DEI LINFOMI (GISL)

*Department of Internal Medicine, Oncology and Radiology Sciences, University of Modena; *Division of Hematology, Ospedale Riuniti, Reggio Calabria; °Department of Oncology and Hematology, Ospedale di Pescara; §Division of Internal Medicine, Section of Hematology, Ospedale Piacenza; @Department of Internal Medicine and Oncology, University of Pavia, IRCCS Policlinico San Matteo, Pavia; #Division of Hematology, S. Maria Nuova Ospedale Reggio Emilia; ^Haematology Unit, University of Pisa; Italy*

ABSTRACT

Background and Objective. **Although in recent years anaplastic large-cell lymphoma (ALCL) has emerged as a distinct clinico-pathological entity, a gold standard for treatment has still not been defined. Goals of our histologic, phenotypic and clinical study were to present clinical findings, treatment outcome and survival rates of a small, but highly homogeneously treated, series of patients.**

Design and Methods. **From April 1991, 36 newly diagnosed adult patients with systemic ALCL CD30+, entered a prospective non-randomized trial in one of the institutions participating in a GISL (*Gruppo Italiano per lo studio dei Linfomi*) study and were treated with a MOPP/EBV/CAD hybrid scheme. Chemotherapy (CHT) was administered every 28 days, for a total of 6 cycles. After CHT, 19 patients received radiation therapy (RT) to the site of previously involved fields. Kaplan and Meier and log-rank tests were used for statistical analysis.**

Results. **The overall complete remission rate was 78%, the partial remission rate was 6%. The overall survival rate at 74 months was 69%. No statistically significant differences in response or survival rates were noted comparing ALCL-HL and -CT subgroups, T+ Null– and B– subtypes, or ALCL-HL and -CT, with different phenotypes. In the analysis of patients with T+ Null phenotype treated with CHT+RT in comparison with B-ALCL patients who had the same treatment, we observed statistically significant differences in the survival rate (p=0.048). No prognostic factors predictive of response or survival were identified.**

Interpretation and Conclusions. **Our results show that using MOPP/ABV/CAD the results, in terms of remission rate and survival, are similar to those obtained with 3rd generation CHT regimens. The diagnosis of T and Null ALCL is the most important prognostic factor, because it is associated with a very good survival, even in patients with a high prognostic index. Finally, we believe that longer follow-ups are needed to evaluate long-term survival and toxicity with different treatments.**

Correspondence: Stefano Sacchi, M.D., Department of Internal Medicine, Oncology and Radiology Sciences, University of Modena, via Del Pozzo 71, 41100 Modena, Italy.
Phone: international +39-059-422175 – Fax: international +39-059-424549 – E-mail: ssacchi@unimo.it

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In 1985, Stein demonstrated the expression of the lymphoid activation antigen CD30/Ki-1 by neoplastic cells.[1] Lymphomas expressing this antigen were defined as Ki-1/CD30+ anaplastic large cell lymphoma (ALCL) and were incorporated into the updated Kiel classification as a separate entity in 1989.[2] Although several ALCL have been reported to express antigens of T-or B-cell lineage, many cases may lack lymphoid antigens (Null type) and rare cases may express both markers.[3] The *Revised European-American Lymphoma* (REAL) classification[4] limited the term of ALCL to T-and Null-cell types, including the B-cell type among the morphologic variants of diffuse large B-cell lymphoma. Four distinct histologic varieties have also been recognized, with the most frequent being the Common type (CT) and the Hodgkin's-related (HR) variety.[5-7] HR-ALCL was reported as a distinct provisional entity in the Real Classification and the term HR was replaced by Hodgkin's-like (HL). Herein we report on 36 adult patients with primary ALCL treated at a GISL (*Gruppo Italiano Studio Linfomi*) center with a MOPP/EBV/CAD hybrid regimen[8] followed by radiotherapy (RT) of the involved field when indicated.

Design and Methods

Patient population

From April 1991 to November 1997, 36 newly diagnosed adult patients with ALCL CD30+, referred to one of the Institutions participating in the GISL study were enrolled in this trial and treated with a MOPP/EBV/ CAD hybrid regimen.[8] The criteria for eligibility included a confirmed histologic diagnosis of ALCL CD30+, stage II to IV according to the Ann

Arbor system[9] or stage I with bulky disease, Karnofsky performance status (PS) over 50, age between 20 to 65 years, and normal cardiac, renal, pulmonary and hepatic functions. The characteristics of the 36 patients are listed in Table 1.

Histopathologic and phenotypic analyses

Slides from routinely paraffin-embedded tissues were stained with hematoxylin-eosin; immunophenotypic analysis was performed on paraffin-embedded sections by Apaap labeling. The diagnosis of ALCL was made according to standard diagnostic criteria,[1] including classic histologic features and reactivity of tumor cells with CD30/Ber-H2. The panel of monoclonal antibodies included CD45/LC, CD30/Ber H2, CD20/L 26, CD45/RO, CD3, CD15, EMA/E29 (DAKO, Glostrup, Denmark).

ALCL were considered as being $CD30^+$ if at least 75% of neoplastic cells stained for the CD30 antigen. Lymphomas were considered of B-cell lineage when tumor cells expressed CD20. They were considered of T-cell origin when tumor cells expressed CD3, or in the absence of $CD3^+$, expressed CD45RO, but not CD20. A lymphoma was determined to be *Null type* when no staining was obtained after testing for B and T lineage.

Staging

Staging procedures included physical examination, LDH determination, HIV, HBV and HCV antibody screening, blood cell and differential counts, liver and renal function tests, computerized tomographic scans of neck, chest, abdomen, and pelvis, and unilateral bone marrow biopsy. Patients were staged according to the Ann Arbor classification.[9]

Treatment protocol

Previously reported[8] as an aggressive regimen for patients with prognostically unfavorable, advanced Hodgkin's disease, the MOPP/EBV/CAD hybrid regimen consists of mechlorethamine (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. Chemotherapy (CHT) was administered every 28 days, for a total of 6 cycles. Drug doses and administration schedules are listed in Table 2. After CHT, 19 patients received RT to the site of previous involved fields, mainly bulky disease in the mediastinum.

Assessment of response

One month after the end of therapy re-staging was performed by physical examination, blood cell and differential counts, liver and renal function tests, LDH evaluation, CT scans of neck, chest, abdomen and pelvis and bone marrow biopsy, in case of positivity at diagnosis. Complete remission (CR) was defined as the disappearance of disease-related signs and symptoms, as well as the normalization of all previous abnormal findings. Partial remission (PR) was defined as a greater than 50% reduction of known measurable

Table 1. Characteristics of the 36 patients with ALCL.

Characteristics	*No. of patients*	*Percentage (%)*
N. of Patients	36	100
Mean age, years	42	
Range	18-73	
Sex		
Male	21	58
Stage		
I and II	18	50
III and IV	18	50
Karnofsky		
50-80%	18	50
>80%	18	50
Bulky disease		
Absent	23	64
Systemic symptoms		
Absent	18	50
Extranodal sites		
Bone Marrow	3	8
Waldeyer's ring	1	3
Spleen	5	14
Liver	1	3
Lung	3	8
Stomach	3	8
Skin	2	6
Histology		
Common	20	55
HR	16	45
Phenotype		
B 10	28	
T + Null	26	72
Treatment		
Chemotherapy	17	47
Chemotherapy + radiotherapy	19	53
International Prognostic Index		
Low + low - intermediate	22	62
High - intermediate + high	14	38
LDH Level		
≤1 x Normal	20	55
>1 x Normal	16	45

Table 2. MOPP/EBV/CAD hybrid regimen: drug doses and time schedule.

Drugs	*Dose (mg/m2)*	*Route*	*Days*	*Cycle*
Mechlorethamine	6	IV	1	cycles 1, 3, and 5, only
Lomustine	100	Oral	1	cycles 2, 4, and 6, only
Vindesine	3	IV	1	
Melphalan	6	Oral	1-3	
Prednisone	40	Oral	1-14	
Epidoxorubicin	40	IV	8	
Vincristine	1.4	IV	8	
Procarbazine	100	Oral	8-14	
Vinblastine	6	IV	15	
Bleomycin	10	IV	15	

disease with disappearance of the systemic symptoms. No response (NR) was defined as less than PR. In 5 patients, with residual masses in the mediastinum, magnetic resonance imaging (MRI) and gallium-67-citrate single-photon emission computed tomography (67 Ga SPECT) were performed. These patients were considered to be in CR when repeated CT scans and/or MRI and/or 67 Ga SPECT did not show changes for at least 12 months.

Statistical methods

All data were analyzed with the Statistical Package for Social Sciences (SPSS).[10] The overall survival was measured from the date of diagnosis to death from any cause or date of last follow-up evaluation. Survival rates were estimated by the method of Kaplan and Meier.[11] Ninety-five percent confidence intervals can be approximated as the life-time table estimates ±1.96 SD. The log-rank test was used whenever appropriate to assess the significance of differences between groups.[12]

Results

At the time of this analysis, the median follow-up period was 35 months, and the maximum follow-up was 7.3 years.

Clinical presentation

The main clinical findings of the 36 patients with ALCL are shown in Table 1. The male/female ratio was 1.4: 1 and the mean age 42 years, but there was a very large range (14-79 y). B symptoms, advanced stages and CT histologic variant of ALCL were observed in about 50% of patients; bulky disease, mainly in the mediastinum was found in 36%. We noted some differences in clinical pictures between patients with CT and HL histologic subtypes and between patients with T + Null and B phenotype subgroups, but these were not statistically significant.

Response to treatment

The complete response rate after CHT was 64% (23/36) and the partial response rate was 22% (8/36), with a major response rate (CR + PR) of 86%; 14% (5/36) of the patients showed no response. After CHT, 19 patients were treated with radiation therapy (RT). One month after RT, 84% (16/19) were in CR and 5% (1/19) were in PR; NR was observed in 11% (2/11) of patients. Thus, the overall response rate in our series of 36 patients after CHT±RT was as follows: CR 28 patients (78%), PR 2 patients (6%) and NR 6 patients (16%) (Table 3). No significant differences were observed between patients with ALCL-HL and -CT, since 81% and 90% obtained CR+PR, respectively (Table 3). It is noteworthy that the 3 patients who relapsed had the ALCL-CT subtype. Nor were any significant differences observed between patients with T+ Null- and B- subtypes, since 88% and 80% obtained CR+PR, respectively (Table 3). Finally, we did not observe statistically significant differences between patients with ALCL-HL and -CT, with different phenotypes (Table 3).

Table 3. Treatment response and survival rate, overall, by histologic and phenotypic subtypes, and by histologic subtypes expressing different phenotypes.

	Patient No.	*CR (%)*	*PR (%)*	*NR (%)*	*Survival Rate (%)*	*95% CI*
Overall	36	28 (78)	2 (6)	6 (16)	69	52-76
HL	16	11 (68)	2 (12)	3 (20)	68	47-89
CT	20	17 (85)	1 (5)	2 (10)	70	43-97
T and Null	26	22 (85)	1(4)	3 (11)	75	56-95
B	10	6 (60)	2 (20)	3 (30)	56	25-87
HL (B-cell)	5	3(60)	1(20)	1(20)	60	19-100
HL (T+Null-cell)	11	8(73)	1(9)	2(18)	72	47-97
CT (B-cell)	5	3(60)	1(20)	1(20)	53	6-100
CT (T+Null-cell)	15	14(93)	0(0)	1(7)	77	46-100

Survival

The survival rate for all the 36 patients at 74 months was 69% (95% CI, 52-76) (Figure 1 and Table 3). We did not find any statistical differences (p=0.4) between survival rates of ALCL-HL and -CT patients, 68% (95% CI, 47-89) and 70% (95% CI, 43-97) respectively (Figure 2 and Table 3). Comparing the group of patients who received only CHT with those who had CHT + RT we did not find statistically significant differences (Figure 3). Figure 4 shows the survival curves of Null+ T- and B- subtype ALCL patients. The differences between subgroups in overall survival were not significant (p=0.12), since B and T+ Null patients showed, at 60 and 81 months, an overall survival rate of 56% (95% CI 25-87) and 75% (95% CI 56-95), respectively. Although no statistically significant differences were observed, there was a ten-

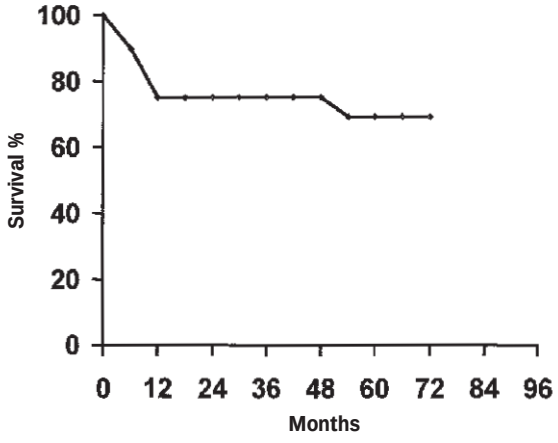

Figure 1. Overall survival curves of 36 ALCL patients.

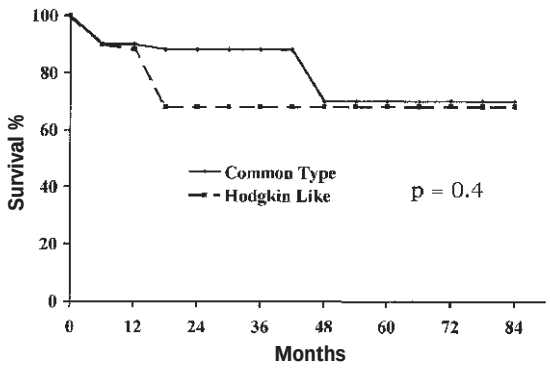

Figure 2. Comparison of survival curves of patients with ALCL-HL and -CT (p=0.4).

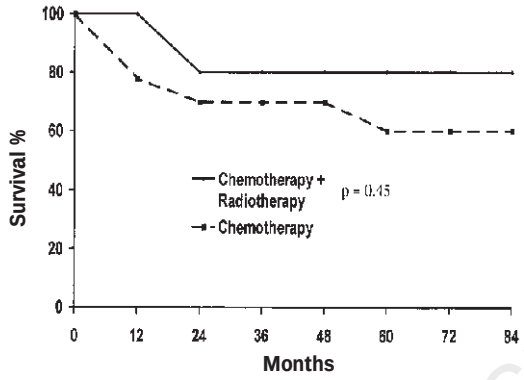

Figure 3. Comparison of survival curves of patients treated with CHT alone and those treated with CHT + RT (p=0.45).

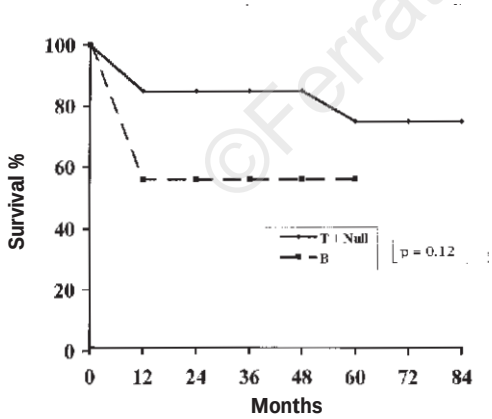

Figure 4. Comparison of survival curves of patients with T + Null- and B-phenotypic subgroups (p=0.12).

dency towards poor survival rate in B-ALCL patients. Analyzing survival distribution for phenotype adjusted for RT (Figure 5), we observed that T+Null patients treated with CHT+RT had an overall survival

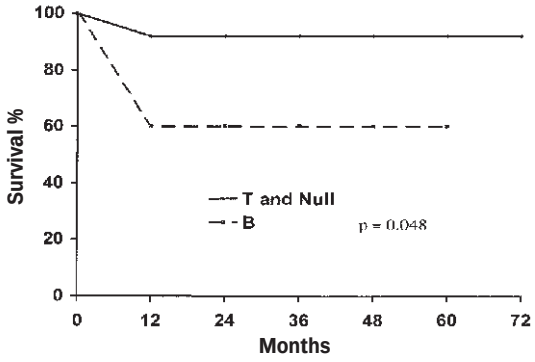

Figure 5. Comparison of survival curves of patients with T + Null- and B-phenotypic subgroups treated with CHT+RT (p<0.048).

rate of 92% (95%CI 79-100) at 74 months, while the B subgroup, treated with the same scheme, had a survival rate of 60% (95% CI 40-100) at 62 months (p=0.048). Finally, we did not find statistically significant differences between patients with HL- and CT-ALCL, with different phenotypes.

Factors predictive of response and survival

The characteristics of patients and their disease are usually considered as prognostic factors: age, presence of B symptoms, I-II versus III-IV stages according to Ann Arbor system,[9] performance status, LDH level, bone marrow involvement, and bulky disease were correlated to response to treatment and survival in univariate analysis. We did not find any correlation between these parameters and treatment outcome or overall survival rate. The *International Prognostic Index* (IPI)[13] developed for aggressive lymphomas in general did not predict survival in our group of patients.

Discussion

In recent years ALCL has emerged as a distinct clinico-pathologic entity, although it is a relatively uncommon disease. In the GISL registry, ALCL accounts for 2.8% of 2871 cases (85 patients) and 4.5% of 1398 cases (63 patients) of NHL enrolled in clinical trials since 1988. Our knowledge of ALCL is limited because of the small number of patients analyzed in the single series and the variety of treatments utilized.[14-29] On the basis of treatment strategies adopted by GISL in January 1991, our 36 adult patients with primary ALCL were treated with a MOPP/EBV/CAD hybrid regimen. This aggressive regimen, originally designed for patients with prognostically unfavorable, advanced HD, was subsequently adopted by GISL for patients with ALCL CD30+, because of encouraging results achieved in HD. The main clinical characteristics of our patients at the time of diagnosis differ slightly from those given in other reports. The male/female ratio was 1.4:1 and the mean age 42 years, but there was a

very large range (14-79 y). B symptoms, advanced stages and CT histologic variant of ALCL were observed in about 50% of patients; bulky disease, mainly in the mediastinum was found in 36%. The overall major response rate in our patients was 84%, which is similar to the rate obtained in other recent series.[27,29] No statistically significant differences in response and survival rate were noted comparing CT- and HL-subgroups, T+ Null- and B- subtypes, and ALCL-HL and -CT, with different phenotypes. Regarding the overall survival, we obtained a rate of 69% at 74 months, again similar to that observed in other ALCL series.[27,29] In particular we did not observe statistically significant differences in survival between patients treated with CHT + RT or with CHT alone. There is, however, a trend towards better survival in patients treated with CHT + RT than in those treated with CHT alone and in patients with T + Null-ALCL in comparison with those with B-ALCL. In the analysis, combining patients with T + Null phenotype treated with CHT + RT in comparison with B-ALCL patients who had the same treatment, we observed statistically significant differences in the survival rate. Our data, showing a tendency towards better results in patients with T+ Null phenotype, support the recent proposition of the REAL classification to consider B-ALCL as a variant of diffuse large B-cell lymphoma, and also support the hypothesis that RT could improve the prognosis of these NHL patients. Further, breaking down patients by histologic subtypes, this regimen, originally designed for aggressive HD appears as effective in ALCL-CT, universally recognized as NHL, as in ALCL-HL, a borderline entity lying midway between NHL and HD.[30] By univariate analysis no factors predicted treatment outcome or survival although other authors[27,29] have found some parameters to be prognostic factors for survival. In agreement with the *Non-Hodgkin's Lymphoma Classification Project*[31] we found that the IPI, developed for aggressive lymphomas in general, did not predict treatment outcome or survival. The diagnosis of T and Null ALCL was the most important prognostic factor, because it was associated with a very good survival, even in patients with a high prognostic index. The good outcome of T + Null-ALCL patients emphasizes the importance of phenotypic studies and does not support the use of intensive chemotherapy with autologous stem cell support.

The MOPP/EBV/CAD hybrid regimen is a valid and relatively well tolerated scheme for the treatment of ALCL, producing results equivalent or superior to 3rd generation regimens of CHT. We did not observe secondary myelodysplasia (MDS), leukemia or second cancers in any patient after a median follow up of 35 months (maximum 7.3 years). Gobbi *et al.*,[32] using the same scheme for the treatment of 145 patients with advanced HD, observed second MDS, secondary lung cancer and colorectal cancer in 2.1%, 0.7%, and 1.4% of patients, respectively, with a median follow-up of 66 months. Recently, Zinzani *et al.*[30] reported the results of a randomized trial of ABVD versus MACOP-B with or without RT in 40 ALCL-HL patients. They showed that, in terms of CR and relapse free survival, patients respond in an equivalent way to both treatments. In the 21 patients treated with ABVD the CR rate was 91% and the median survival rate at 37 months was 90%. ABVD seemed to induce higher response rate in ALCL-HL than in advanced HD, in which a CR rate of 82% was observed.[33] The 11 ALCL-HL patients with a T+ Null phenotype enrolled in our trial had a CR rate of 73% (major response 82%) and an overall survival rate of 72% at 70 months. We agree with this idea of testing less aggressive regimens, such as ABVD, in order to avoid the risk of over-treating this group of patients with a surprisingly good survival. We do, however, believe that longer follow-ups are needed to evaluate long-term survival and toxicity with different treatments, such as aggressive or standard protocols for HD or 3rd generation CHT regimens for NHL.[34,35]

Contributions and Acknowledgments

All the authors contributed to the design of the study and to recruiting patients. GL, CF and SS performed the analysis and interpretation of data, and wrote the paper. All the authors gave their critical contribution to the manuscript and approved its final version. VS is a GISL supervisor.

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Disclosures

Conflict of interest: none

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The initial follow-up of 10 out of the 36 patients was published in 1995 (ref. #24).

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