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Mantle cell lymphoma: a retrospective study on 27 patients. Clinical features and natural history

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Abstract

Background and Objective. **Mantle cell lymphoma (MCL) is a separate histological and clinical entity recently recognized in the new revised *European-American Lymphoma Classification*. Little information exists regarding its therapy. We report the results of a retrospective study of 27 patients affected by MCL evaluating the clinical characteristics and the results of different therapeutical options used during the period of observation.**

Design and Methods. **From 1983 to 1993, we observed 27 patients affected by MCL according to the criteria proposed by *European Lymphoma Task Force* in a revision of 55 cases classified as NHL E according to Working Formulation (WF) criteria. We analyzed the clinical characteristics, the prognostic factors and the O.S. of these patients.**

Results. **The clinical characteristics of our patients (pts) are similar to those observed in other series: male prevalence, median age 62 years, B symptoms in 9 cases, P.S. > 2 in 11 cases, 3 pts were in stage I and II, 4 in stage III, 20 in stage IV; 18 pts had a bone marrow involvement, 13 pts had spleen enlargement and 14 had extranodal localization; 8 pts had bulky tumor and 5 had LDH above normal. The CR rate was 51,8%, the median O.S. was 43 months, and DFS was 18 months; the pts without bulky disease and with localized disease had a better CR rate. The inclusion of an anthracycline in the regimen did not affect the results.**

Interpretation and Conclusions. **Our results were not divergent from those present in literature. The mantle cell lymphoma is an incurable and highly aggressive disease. Autologous bone marrow transplantation as support of high dose chemotherapy or allogenic bone marrow transplantation may be a *chance* for some patients, but not for the majority of patients, which are older than 65 years. Studies of a larger series and different therapeutical approaches, ie using biological modifiers in association or as maintenance after chemotherapy are essential.**

Key words: mantle cell lymphoma, chemotherapy

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Mantle cell lymphoma (MCL) has recently been recognized as a separate histological and clinical entity,[1,2] and as such, it appears in the Revised *European American Classification of Lymphoid Neoplasms*.[3,4]

This non Hodgkin's B cell lymphoma (NHL) is constituted of small to medium sized cleaved cells, with a characteristic phenotype: $CD5^+$, $CD10^-$, $CD23^-$, $CD20^+$, high surface expression of IgM and IgD and more expression of λ light chains than κ.[5-8]

The data indicate that mantle cell may be the neoplastic counterpart of a B cell subset normally residing in the follicle mantle.[9]

MCL is associated with a chromosomal abnormality: the t(11;14) (q13; q32) translocation, which results in the rearrangement of the BCL1 locus and the over expression of CCND1 protein that usually is not expressed in the lymphatic ganglion.[1,10-17]

MCL is characterized by a generalized lymphadenopathy and a frequent, often extensive, involvement of the spleen, liver and especially bone marrow.[9] It represents 2-9% of all NHL and it seems that this incidence is increasing with a continuous trend.[18-20] There is usually male prevalence (M/F=2/1) and it often shows up in patients older than 60 years.[18] It is often localized at the digestive system (stomach, ileum, colon and rectum).[21]

Even if MCL's clinical and pathological features have already been well acquired, there is a little information about MCL's therapy.

The aims of this study are to analyze, retrospectively, the efficacy of anthracycline containing chemotherapy (CT), and evaluate the prognostic factors for response to treatment.

Patients and Methods

Samples of all patients treated at the *Divisione di Ematologia, Azienda Ospedaliera S.Giovanni Battista, Turin*, from 1983 to 1993 and diagnosed as small cleaved cell, diffuse lymphoma (E) according to the Working Formulation,[21] were reviewed by a single pathologist.

Cases with adequate and well preserved material, according to the *European Lymphoma Task Force* criteria, typical cytological criteria and/or complete and typical characteristic immunophenotype $CD20^+$,

$CD5^+$, $CD10^-$, $CD23^-$ were considered eligible.

Of the 55 cases reviewed, 27 (49%) were considered as MCL. Diagnosis of MCL was based on morphological and immunophenotypical criteria. The last samples were classified as lymphomas of low grade of malignancy: lymphocytic lymphoma (16%), MALT (16%), immunocytoma (9%), follicular lymphoma (2%), other types (4%) and not otherwise classifiable (4%).

Patients were clinically staged according to the *Ann Arbor Classification*. Staging procedures included physical examination, routine laboratory tests with special regard for LDH and β2 microglobulin (whenever available), bilateral bone marrow aspiration and biopsy, chest x-ray, and computerized tomographic scan (CT) of the chest, abdomen and pelvis.

Bulky disease was defined as a mediastinal mass more than 0.33 of the chest diameter, or mass larger than 10 cm. The *International Prognostic Index*, according to the Shipp's criteria,[22] was employed to identify 4 different groups: low, intermediate low, intermediate-high and high-risk.

Tumor burden was also valued, defined as low or high according to the number of extensive nodal areas and extranodal sites, as proposed by MDAH in 1986.[23]

None of the patients were pretreated and treatment was heterogeneous as expected. Seventeen patients received CHOP regimen (cyclophosphamide, vincristine, adriamycin, prednisone)[24] and 2 of them received extended field radiotherapy as well; there was one splenectomy: 4 patients received CVP (cyclophosphamide, vincristine and prednisone)[25] and 2 of them also received involved field radiotherapy. In 2 cases treatment was chlorambucil and prednisone, 2 patients received PVEBEC (prednisone, vinblastine, epirubicin, bleomycin, etoposide and cyclophosphamide) treatment,[26] 1 of them also received extended field radiotherapy, 1 patient received VACOP (doxorubicin, cyclophosphamide, etoposide, vincristine and prednisone)[27,28] and another splenectomy alone.

Complete remission (CR) was defined as the disappearance of all detectable signs of the disease for longer than 2 months; a partial remission (PR) was defined as a 50% or greater decrease in the sum of the products of the maximum perpendicular diameters of all measured lesions lasting for at least 4 weeks. Failure was defined as anything less than PR.

Overall survival (OS) and disease-free survival (DFS) were calculated according to the Kaplan and Meyer method. In particular, OS was calculated from the time of diagnosis to death or last follow-up – alive or lost, and DFS from the date of achievement of CR to the date of relapse.

All calculations were done through the BMDP program, developed at the *Health Science Computing Facility, University of California, Los Angeles (National Institutes of HEALTH) Special Research Resources*.

Results

The clinical characteristics of the 27 patients are listed in Table 1.

They included a preponderance of male gender (n=19), a median age of 62 years (range 38-82), B symptoms in 8 cases and P.S. >2 in 8 cases.

The disease was stage I and II in 3 patients, stage III in 4, and IV in 20 ; 18 subjects had a bone marrow involvement (67%), 13 had spleen enlargement and other extranodal localization, included liver (7 patients), lung (2), stomach (1), kidney (1), skin (1), parotitis (1) and breast (1).

Table 1. Clinical characteristics of 27 patients.

	Percentage	Patients
Age		
< 60 years	37	10
> 60 years	63	17
Sex		
Male	70	19
Female	30	8
PS		
≤ 1	70	19
≥ 2	30	8
Symptoms		
A	70	19
B	30	8
Stage		
I	4	1
II	7	2
III	15	4
IV	7	2
IV+BM	67	18
Bulky		
yes	30	8
no	70	19
Splenomegaly		
yes	52	14
no	48	13
Tumor burden		
low	56	15
high	44	12
IPI		
0	3.5	1
1	14;5	4
2	41	11
3	26	7
4	15	4
LDH		
< 500	81.5	22
> 500	18.5	5
Chemotherapy (26 patients)		
CHOP *VACOP* *P VEBEC*	75	20
LEUK	20	6

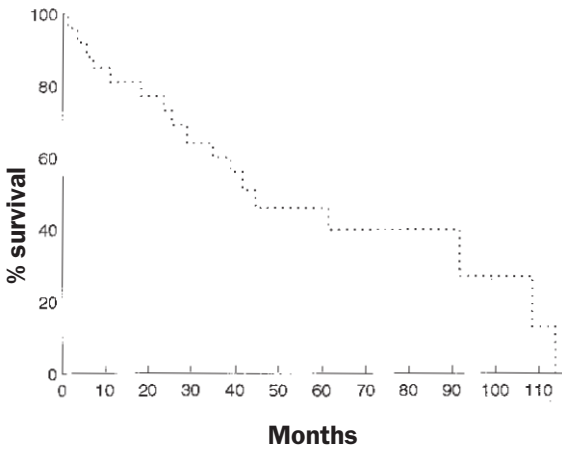

Figure 1. Overall survival of 27 patients affected by mantle cell lymphoma.

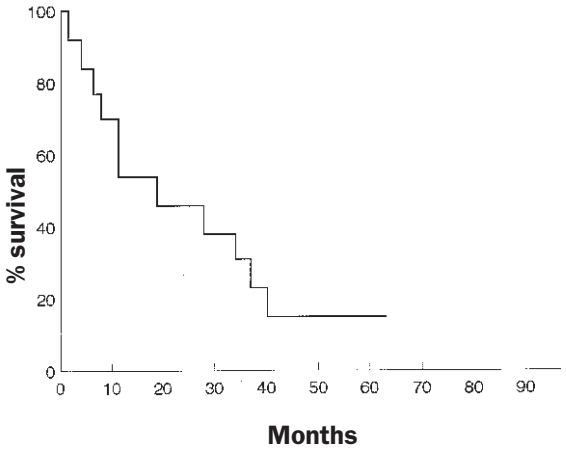

Figure 2. Disease free survival of 14 patients who achieved complete remission.

Bulky tumor (>10 cm) was noted in 8 patients (30%) and an elevate LDH in 5/27 patients (18.5%).

According to the *International Prognostic Index*, 41% were classified as intermediate-high or high-risk.

The CR rate was 51.8% independently from therapy used; the median OS was 43 months, but none of the patients were alive after a 110 months follow-up (Figure 1). The median DFS was 18 months, but only 15% of patients were without lymphoma at a 90 month follow-up (Figure 2).

The I-III stage patients showed a better CR rate (71%) (p=0.005) compared to advanced stage (45%). The presence or the absence of bulky areas did not affect the CR rate. The CR rate was 50% in younger patients versus 53% in patients over 60 years (p=ns).

The CR rate was 47% for men versus 63% for women (p=ns).

The inclusion of anthracycline in the treatment protocol did not affect the CR rate: 45% of patients treated with chemotherapy which consisted of an anthracycline-based regimen achieved CR versus 67% who received a chemotherapy without anthracycline (p=ns). Also OS and DFS were not different compared to patients receiving anthracycline regimens, even if little numbers do not allow too many conjectures.

Discussion

The term *mantle cell lymphoma* has been introduced by the *International Lymphoma Study Group*[4] to clarify the great confusion among similar entities: *intermediate lymphocitic lymphoma*, *lymphocytic lymphoma of intermediate differentation*, *mantle zone lymphoma* and the European *centrocytic lymphoma*.[1,2] It has a particular phenotype, cytogenetic and molecular biology, as stated in the introduction.[5-8]

This distinct clinicopathological entity accounts for 2 to 10% of all NHL. The incidence seems lower in USA than in Europe, affects patients older than 60 years and prevails in men more than women. The clinical characteristics of our patients, as in Table 1, are quite similar to those previously reported in the pertinent literature, for instance those presented by the *European Lymphoma Task Force at the Workshop on Mantle Cell Lymphoma*[29] as already mentioned in the introduction.

In our study, the median survival was 38 months, the overall survival had a median of 42 months and no patient was alive after a 110-month follow-up. DFS had a median of 12 months, but at a 90-month follow up the disease free survival was 15%.

These results do not differ from those presented at the *Workshop on Mantle Cell Lymphoma by the European Lymphoma Task Force* (ELTF), the overall survival was about 3 or 4 years, as found in retrospective analyses presented by different groups (A.T. Lister, D.D. Weisenburger, J.C. Kluin-Nelemans, E. Zucca, and B. Coiffier).[29]

In the *Revised European Lymphoma Classification,* MCL is presented as *an incurable and highly aggressive lymphoma with a median survival of 3-5 years in its classic form*.[3]

According to the ELTF, the main prognostic factors are elevated LDH and/or β2 microglobulin, poor performance status, advanced stage and advanced age (>60 or 65 years).[29]

Among prognostic characteristics, only advanced stage and bulky disease negatively affected CR rate. No difference has been identified in the CR rate between regimens containing or not containing anthracycline. With respect to the different treatments employed, only Zucca[19] seems to underline the advantage of the regimens containing anthracycline.

Our results were not remarkably divergent from those presented at the *International Conference on Malignant Lymphoma* held in Lugano (1996): the CR rate

Table 2. Prognostic characteristics and CR rate of 27 patients.

	Percentage	Patients	p value
Age			
< 60 years	50	5	
> 60 years	53	9	ns
Sex			
Male	47	9	
Female	63	64	5
P.S.			
≤ 1			ns
≥ 2	9		
Symptoms			
A	53	36	5
B	/		
Stage			
II+III	71	5	
IV	45	9	p=0.005
Bulky			
No	42	8	
Yes	75	6	ns
I.P.I.			
< 3	63	10	
> 3	36	4	ns
LDH			
< 500	59	13	
> 500	20	1	ns
Anthracyclin			
No	67	4	
Yes	45	9	ns

varies from 20 to 60%, the OS varies from 26 to 61 months, and the DFS varies from 13 to 20 months, as reported by most authors. The variations among different series are quite probably due to the different clinical characteristics of the diagnosed patients.[29-32]

In our department, one patient has been treated with autologous bone marrow transplantation during CR and he is alive and well 5 years from ABMT; another patient was transplanted with allogeneic bone marrow in persistence of NHL, and he is alive with persistent illness with a FU of 2 years.

Some authors, as Tarella *et al*.,[33] Stewart *et al*.,[34] or Martinez *et al*.[35] have started the treatment with high dose chemotherapy supported by autologous bone marrow transplantation or bone marrow stem cells even in patients affected by MCL, and they report the achieving of CR in a large number of patients. The choice of high dose chemotherapy requires studies on a higher number of patients. However, it cannot be applied on patients over 60.

Another choice might be the allogenic bone marrow transplantation as reported by Tarella *et al*.,[33] but so far the experience is limited and furthermore, it cannot be used in elderly patients.

The therapeutic experience with new purine analogues (Fludarabine and 2-CDA) and with monoclonal antibodies of the CAMPATH family is limited and thus far disappointing.[28,36]

Therefore, MCL is one of the worst prognosis categories of all the common NHL, and for such a histotype, no treatment can obtain satisfactory results.

As conventional therapy has proven ineffective in curing these patients, different therapeutical approaches and studies on larger series are mandatory.

Contributions and Acknowledgments

MB, CR, RF revised the patients, collecting clinical data. DN and GP diagnosed and revised histological preparations. BB, RC, LO collaborated on the cure and the follow-up of the patients. UV and LR revised the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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