RICHTER'S SYNDROME IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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ABSTRACT

Objective: The development of a higher grade lymphoma in patients with chronic lymphocytic leukemia (CLL) is defined as Richter's syndrome (RS). The aim of this study was to analyze all CLL patients seen at Marmara University Hospital during 7 years of follow up in order to determine the incidence, clinical features and treatment outcome of patients who transformed to RS.

Patients and Method: Fifty four patients with CLL were evaluated in this retrospective study, where records of all patients with CLL, who are followed up at the haematology out-patient clinics during 7 years, were examined in order to determine whether Richter transformation had occurred at any time during the course of the disease.

Results: Richter's syndrome was observed in 3 out of 54 patient, giving an incidence of 5.6%. The presenting features of RS have been systemic symptoms, rapidly progressive lymphadenopathy, and elevation of lactate dehydrogenase LDH. None of the patients responded to systemic chemotherapy and the median survival was only 4 months following the diagnosis of RS.

Conclusion: Early diagnosis of RS is possible with the recognition of the warning symptoms and signs, but treatment remains unsatisfactory. The study highlights the need to develop new strategies for the successful treatment of RS.

Key Words: Richter's syndrome, Chronic Lymphocytic Leukemia

INTRODUCTION

Development of a higher grade malignant lymphoma in a patient with chronic lymphocytic leukemia (CLL) was first described by Richter in 1928 (1). Previous studies report the development of a higher grade lymphoma in 3% to 10% of CLL patients (2,3). True incidence of this transformation may be higher, as post-mortem examinations are not routinely performed in all CLL patients in order to search for occult or missed high grade lymphoma. The morphologic transformation of CLL, which usually occurs months to years after the diagnosis of CLL, is associated with clinical progression and it has been designated as Richter's syndrome (RS). Some investigators have included patients with the diagnosis of histiocytic lymphoma (2,4) and Hodgkin's disease (5) following CLL in the definition of RS. Systemic symptoms, rapidly progressive lymphadenopathy, extranodal disease, monoclonal gammopathy, and elevation of lactate dehydrogenase (LDH) over twice the normal value have been described as the clinical features which characterize the development of RS in a patient with CLL (2,3,6).

The aim of this study was to analyse all CLL patients seen at Marmara University Hospital during 7 years of follow up in order to determine the incidence, clinical features, laboratory findings and treatment outcome of patients who transformed to RS.

PATIENTS AND METHODS

Fifty four patients with CLL were evaluated in this retrospective study, where records of all patients with CLL, who are followed up at the haematology out-patient clinics, were examined in order to determine whether Richter transformation had occurred at any time during the course of the disease.

International Working Group on CLL (IWCLL) guidelines were applied for the diagnosis of CLL (7). Morphologically the lymphocytes had to be mature and the bone marrow aspirate had to show that greater than 30% of all nucleated cells were lymphocytes. CLL

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classification was determined according to the Rai staging (8).

Diagnosis of RS was established according to the clinical features as previously described and also pathologically (2,3,6). The pathological diagnoses were based on lymph node biopsies in two patients, and biopsy of a paravertebral mass at the time of presentation of CLL in one patient.

RESULTS

Richter's syndrome was observed in 3 out of 54 patients, giving an incidence of 5.6%. Clinical data for these patients is illustrated in Table I. Mean age of the CLL patients was 65 years. Thirty one patients were male and 23 patients were female. Majority of the patients (25/54) were Rai stages I and II. Fourteen patients were lost to follow-up. Median survival in the remaining patients was 38 months. In addition to the 3 patients, who transformed to RS, 5 CLL patients had transformed to prolymphocytic leukemia (PLL). Median duration of time from diagnosis of CLL to RS was 27 months. The outstanding clinical features of RS prior to diagnosis were systemic symptoms of malaise, weakness, fever and weight loss, rapidly progressive lymphadenopathy and elevation of the LDH to more than twice the upper limit of normal in all three patients (Table II). The first two patients were treated with Mini-BEAM (carmustine, etoposide, cytarabine, melphalan), and the third patient, who presented with a paraspinal mass, received three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. None of the patients responded to the systemic chemotherapy. The first patient died following 3 months, and the other two patients died following 4 months after the diagnosis of RS.

Table I. Clinical features of 54 patients with CLL

Clinical features	No.
Mean age (years)	65±9
Sex	
Female	23
Male	31
Rai staging	
0	12
I, II	25
III, IV	17
Bulky disease	9
Median survival (months)	38
Lost-to-follow-up	14
Infectious complications	20
Immune Hemolytic Anemia	1
Immune Thrombocytopenia	1
Total number of deaths	13
due to disease progression	8
other	5
PLL transformation	5
Richter's Syndrome	3

Table II. Characteristics of 3 patients with Richter's Syndrome

Patient	1	2	3
Age (years)	61	48	70
Sex	Female	Male	Male
Rai stage	II	II	III
Prior regimens	chlorambucil adriablastina, ara-c	chlorambucil, CHOP, fludarabine	None
Reason for prior chemotherapy	Rapid lymphocyte doubling time	Rapid lymphocyte doubling time	–
Systemic symptoms	Yes	Yes	Yes
Bulky disease	Yes	Yes	Yes
Extranodal disease	No	No	paravertebral mass
WBC count at RS (10^9/l)	33.6	75.1	11.3
LDH>twice normal	Yes	Yes	Yes
Monoclonal gammopathy	No	No	No
Lymph node pathology	accelerated phase CLL with prolymphocytes and immunoblasts	diffuse, high-grade malignant lymphoma	Paravertebral mass high-grade malignant lymphoma
Treatment for RS	Mini-BEAM	Mini-BEAM	CHOP
Survival (months)	3	4	4

WBC: white blood cell; LDH: lactate dehydrogenase;
ara-c: cytosine arabinoside; CHOP: cyclophosphamide, adriamycine, vincristine, prednisone;
Mini-BEAM: carmustine, etoposide, cytarabine, melphalan

DISCUSSION

Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative disorder characterized by proliferation of small, mature-appearing lymphocytes, usually of B-cell type. CLL may transform into large cell lymphoma (LCL) in 3-5%, prolymphocytic leukemia (PLL) in 10%, acute lymphoblastic leukemia (ALL) in less than 1%, and multiple myeloma in less than 1% of these patients (9). Isolated cases of CLL, transforming into small noncleaved cell lymphoma, lymphoblastic lymphoma, hairy cell leukemia, and Hodgkin's disease have been reported (10). The development of a second higher-grade lymphoma in patients with pre-existing CLL is called Richter's Syndrome (RS).

The incidence of RS in CLL patients in this study was 5.6%, which is consistent with previous researches reporting an incidence in the range of 3-10% (2,3). The three patients who underwent Richter's transformation, developed systemic symptoms, progressive lymphadenopathy, followed by rapid clinical deterioration, chemotherapy resistance and death within 4 months. Two patients had Rai stage II, and one patient had Rai stage III at the time of transformation. Previously series illustrate that staging

of the CLL patients may not be relevant, as even those patients with minimal residual disease can transform to RS (3).

Prolonged or intensive cytotoxic therapy for either neoplastic or non-neoplastic conditions is known to increase the risk of developing a heamatological malignancy. Acute myeloid leukemia, diffuse histiocytic lymphoma, diffuse undifferentiated lymphoma, and primary intracranial histiocytic lymphoma are malignancies which are most clearly related to prior cytotoxic and/or radiation therapy. Although it is possible that prior cytotoxic therapy may increase the risk of RS transformation in some patients with CLL, Trump et al showed that nearly one-third of RS patients had never received treatment for CLL (2). In our study, patient 3 received no treatment for CLL prior to the Richter's transformation, but he still died 4 months following the diagnosis despite therapy. It is therefore unlikely that previous chemotherapy is a significant influencing factor in the transformation of CLL to RS. RS may occur as a result of a transformation of the CLL clone, or it may occur as a malignancy arising from a second distinct and independent clone (11, 12)

The prognosis of patients who progress to RS is much worse than the prognosis of uncomplicated CLL. This was illustrated by our study, which showed that the median survival in RS patients was 4 months despite treatment in comparison with the remaining CLL patients, whose median survival was 38 months. None of the RS patients in this study achieved a remission with chemotherapy. Trump et al's study supports the findings of this report by stating a median survival of 4 months, and a poor response to chemotherapy with only 14% complete remission rate for the RS patients (2). Those few patients who respond to chemotherapy appear to have longer durations of survival even though the chances of a cure is a rarity (2,13). This is in contrast with the diagnosis of primary high grade lymphoma, which is curable in nearly 40% of the patients (14).

In conclusion, early diagnosis of RS is possible with the recognition of the warning symptoms and signs, but treatment remains unsatisfactory. The study highlights the need to develop new strategies for the successful treatment of RS.

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