Mediastinal Large-B-Cell Lymphoma With Sclerosis: A Clinical Study of 21 Patients

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We report the clinical findings of 21 consecutive patients affected by mediastinal large B-cell lymphoma with sclerosis. This type of lymphoma is a recently described histopathologic entity characterized on clinical grounds by distinctive features, which, according to our series, can be summarized as follows: young age (median, 30 years; range, 15 to 42 years), prevalence of females over males (15 *v* six), rare occurrence of superficial lymph node enlargement (three of 21 patients), and involvement of unusual extranodal sites (kidney six, adrenal cortex two patients). The clinical course appears to be closely related to treatment. In fact, complete remission (CR) was not obtained in the six patients submitted to conventional cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP plus bleomycin (CHOP-Bleo) regimens until 1985, as opposed to 13 CRs reached in the 15 patients subsequently treated with more aggressive regimens after 1985 (methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin [MACOP-B], 12 patients; methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone [M-BACOD], two patients; and vincristine, cyclophosphamide, fluorouracil, cytarabine, doxorubicin, methotrexate, and prednisone [F-MACHOP], one patient; plus involved-field radiotherapy, 10 patients). Among the 13 patients who achieved a CR, only one relapse was observed at 10 months. The median overall survival of complete responders after an observation period of 11 to 69 months has not yet been reached, and the event-free survival curve indicates that 90% of patients who achieve CR may be potentially cured. ***J Clin Oncol 8:804-808. © 1990 by American Society of Clinical Oncology.***

RECENT REPORTS described clinically aggressive mediastinal non-Hodgkin's lymphoma (NHL) in young adults, histologically characterized by a diffuse, large-cell proliferation with sclerosis.[1-4] A number of immunophenotypic and genotypic studies have demonstrated the B-cell origin of this histologic entity, which is now referred to as mediastinal large-B-cell lymphoma with sclerosis.[5-10]

Most previous reports have been focused on the histopathologic pattern, and relatively little information is available about the clinical features and the pattern of therapeutic response of this newly recognized lymphoma.[5-9,11] More clinical data are described in a recent series by Jacobson et al.[12] Although the B nature of the lymphoma is not mentioned in this report, it probably describes the same entity observed in our study.

In the present study, we report a series of 21 patients affected by mediastinal large-B-cell lymphoma treated in our institution since 1982, paying special attention to the clinical aspects at presentation and to the response to two different therapeutic approaches.

PATIENTS AND METHODS

We reviewed the medical records of 21 consecutive adult patients (at least 15 years of age) observed between February 1982 and October 1988 at the Hematologic Department of Verona University, Verona, Italy, with the histologic diagnosis of mediastinal large-B-cell lymphoma.

The histologic diagnosis was made according to the previously described criteria[8]: diffuse histologic pattern without evidence of nodularity, constant presence of thin-band compartimentalizing sclerosis, frequent necrosis, and neoplastic cells predominantly of large size with clear and abundant cytoplasm and round or ovoid nuclei with high mitotic activity, as proved also by the use of Ki-67 antibody. The diagnostic material was obtained through thoracotomy or mediastinoscopy in most patients (18 of 21), since superficial lymph node involvement, always in the lower supraclavicular site, was observed at presentation only in three cases. The lymphoid nature of the disease and its B-cell affiliation was proved in all cases by immunohistochemical analysis on paraffin sections and, when available (17 of 21 patients), also on cryostat sections using avidin-biotin immunoperoxidase

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technique. Briefly, the neoplastic cells were CD45+, exhibited B-cell lineage markers (CD20+, CD22+), and lacked T-cell markers such as CD3, CD5, and CD7. The neoplastic cells were also negative when investigated with antibodies specific for TdT, CD1, cytokeratin, and placental alkaline phosphatase (PALP). In six patients, the B-cell nature of neoplastic cells was proved also by the Southern blot analysis, which demonstrated a clonal pattern of rearrangement of genes encoding for the μ chain of immunoglobulins.[12] Using the above diagnostic approach, we were able to change the erroneous histologic diagnosis previously made in eight patients (thymoma in four patients, Hodgkin's disease in two, malignant dysgerminoma in one, and mediastinal seminoma in one).

Staging

The patients' clinical stage was defined according to the Ann Arbor classification on the basis of physical examination, routine laboratory tests, bone marrow aspirate and trephine biopsy, chest x-ray, echo scan of the abdomen, computed tomographic (CT) scan of the thorax and abdomen, and lumbar puncture. Bulky disease was defined as mediastinal mass diameter measuring longer than 10 cm. Complete remission (CR) was defined as disappearance of all detectable signs of the disease lasting longer than 3 months. Partial remission (PR) was defined as a reduction of at least 50% of the measurable tumor. Overall survival and event-free survival were calculated according to the Kaplan-Meier method.

Treatment

Five patients had been previously treated elsewhere. Three of them had received involved field radiotherapy after a partial resection of the mediastinal mass, on the basis of an erroneous diagnosis of thymoma. They came to our attention after relapses occurred outside the irradiation field. A fourth patient with a previous diagnosis of thymoma received combined radio-chemotherapy. The fifth patient had been treated for Hodgkin's disease with a combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimens, followed by methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) when the correct diagnosis of large B-cell lymphoma was made.

Six patients observed until 1985 were given cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (four patients) or CHOP plus bleomycin (CHOP-Bleo) (two patients) regimens: five of them had not been previously treated.

The 15 more recent patients, including four pretreated patients observed at relapse after radiation therapy (two patients), chemotherapy (one patient) or chemo-radiotherapy (one patient), received aggressive chemotherapy regimens: MACOP-B 12 patients,[13,14] methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) two patients,[15,16] vincristine, cyclophosphamide, fluorouracil, cytarabine, doxorubicin, methotrexate, and prednisone (F-MACHOP) one patient.[17] All these patients are assessable for response. The dosages of administered first-line chemotherapy were compared with the full dosages for the used regimens. After the achievement of CR, the 10 patients with localized disease (stage I or II) who had not been previously irradiated received an involved-field mediastinal radiotherapy as consolidation (mean dosage, 38 Gy; range, 33 to 40). Seven of these patients had bulky mediastinal mass.

Various polychemotherapeutic regimens, including second-line drugs (cytarabine, etoposide, ifosfamide, procarbazine, cisplatin) and/or involved-field radiotherapy were used in patients who did not achieve a CR.

RESULTS

Fifteen of the 21 patients were females, and six were males (F/M ratio: 2.5). The median age at diagnosis was 30 years (range, 15 to 42). This group of lymphomas constitutes the 7.5% of 280 NHL observed in the same period in our department.

The sites of involvement at presentation and the clinical stage are reported in Table 1. Two patients were asymptomatic at diagnosis, and the mediastinal mass was discovered during a routine chest x-ray examination. The remaining 20 patients were symptomatic. The mean time elapsed between the initial symptoms and the diagnosis was 37 days (range, 15 to 90). In 16 of 21 (76%) patients, bulky mediastinal disease was present. Eleven patients (52.3%) had superior

Table 1. Disease Sites at Presentation in 21 Patients With Mediastinal Large-B-Cell Lymphoma According to Stage

Stage	Patients	Bulky	Pleura/ Pericardium	Parasternal	Lung	Liver	Kidney	Adrenal Cortex
IA	1	—	—	—	—	—	—	—
IIA	4	4/4	—	—	—	—	—	—
IIEA	3	2/3	1/3	2/3	2/3	—	—	—
IIB	2	1/2	—	—	—	—	—	—
IIEB	3	3/3	2/3	1/3	—	—	—	—
IVA	5	4/5	2/5	—	3/5	2/5	3/5	2/5
IVB	3	2/3	2/3	—	—	1/3	3/3	—
Total	21	16 (76%)	7	3	5	3	6	2

vena cava syndrome (SVCS); three patients had fever and weight loss or sweats or asthenia, and four patients had thoracic pain. In five patients, the mediastinum was the only site of involvement. In eight patients, contiguous tissues (pleural and/or pericardial effusion) and/or lymph nodes were infiltrated. In the eight patients classified as stage IV, the kidney was the most common site of parenchimal involvement (six patients); adrenal cortex (two), liver (three), and lung (three) were the other sites of parenchimal involvement. Bone marrow or CNS involvement were never documented at presentation.

Response to Therapy

The therapeutic results are shown in detail in Table 2. Overall, 13 of 21 (61.9%) patients achieved a CR. The CR was obtained in 11 of 16 previously untreated patients (64.7%) and in two of five previously treated cases.

The CR was never obtained with conventional chemotherapy regimens (CHOP or CHOP-Bleo) used in six patients until 1985. A partial response was obtained in four patients (median survival, 17 months; range, 1 to 25). Two patients failed to respond, and both died within 6 months. All the patients received full dosages of chemotherapy.

Thirteen of 15 patients (86.6%) treated with aggressive regimens achieved a CR. Of these patients, all the 13 patients who had not received previous chemotherapy achieved CR. We observed only one relapse at 10 months that occurred in sites external to the radiotherapy field (kidney and abdominal lymph nodes). The patient subsequently died because of disease progression.

The median follow-up of the patients who achieved CR is 39 months (range, 11 to 69). The overall actuarial survival curve of all patients is shown in Fig 1. The event-free survival curve of the 13 patients who had not received previous chemotherapy and were treated with aggressive regimens is shown in Fig 2. The median overall survival has not yet been reached. The event-free survival curve of 13 patients treated with aggressive regimens who did not receive previous chemotherapy shows a plateau of about 90% (Fig 2).

DISCUSSION

The mediastinal large-B-cell lymphoma with sclerosis has been recently described as a distinct histopathologic entity.[5-11] It is characterized by a diffuse, large, clear-cell proliferation and by the constant presence of sclerosis. The sclerosis was also observed in the three patients whose diagnosis was performed by examination of supraclavicular lymph nodes contiguous to the mediastinal mass. The B origin of the neoplastic cells has

Table 2. Outcome of 21 Patients With Mediastinal Large-B-Cell Lymphoma With Sclerosis According to Treatment

Age/Sex	Stage	Previous Therapy	Initial Treatment	Response	Follow-up (Months)
23/M	IVB*	—	CHOP	PR	15
22/F	IIEB*	—	CHOP-bleo	NR	6, 5
15/F	IIEA*	—	CHOP	NR	6
28/M	IIEA*	—	CHOP-bleo	NR	17
32/F	IVA*	Mediastinum RT	CHOP	PR	15
21/M	IVB*	—	CHOP	PR	25
33/F	IVA*	Mediastinum RT	m-BACOD	CR	69+
26/F	IIEA	—	F-MACHOP + RT	CR	52+
37/M	IIA*	—	m-BACOD + RT	CR	47+
30/M	IA	—	MACOP-B + RT	CR	46+
42/F	IIA*	—	MACOP-B + RT	CR	41+
30/F	IVA	—	MACOP-B	CR	40+
23/M	IVA*	Mediastinum RT	MACOP-B	CR	34+
35/F	IVB	VCR + Plat + CTX + ADM + RT	MACOP-B	PR	11
25/F	IIB	—	MACOP-B + RT	CR	30+
39/F	IIA*	—	MACOP-B + RT	CR	29+
41/F	IIEB*	—	MACOP-B + RT	CR	17
25/F	IIB*	—	MACOP-B + RT	CR	26+
27/F	IVA*	MOPP/ABVD	MACOP-B	PR	16
30/F	IIEB*	—	MACOP-B + RT	CR	15+
30/F	IIA*	—	MACOP-B + RT	CR	11+

Abbreviations: VCR, vincristine; Plat, cisplatin; CTX, cyclophosphamide; ADM, doxorubicin; RT, radiotherapy; NR, no response.
*Bulky disease.

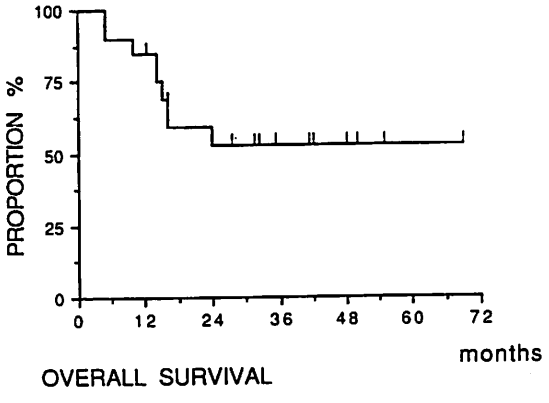

Fig 1. Survival of 21 patients with mediastinal large-B-cell lymphoma with sclerosis.

been proven by immunologic and genotypic analyses.[18] The hypothesis that this neoplasm can originate from the B-cell population normally present in the thymus has been recently formulated.[6,10,19] Due to the difficulties often arising in the differential diagnosis with thymoma, mediastinal seminoma, Hodgkin's disease and, more rarely, with anaplastic carcinoma,[6,7,10] immunohistochemical tests are of great importance for diagnostic and therapeutic purposes.[6,8]

The analysis of our series confirms that, as well as showing a specific histopathologic and immunohistochemical pattern, this type of lymphoma appears also to have some characteristic clinical features.

First, there is a strong prevalence of females over males, and the age at onset is younger as compared with all aggressive NHL in adult patients considered together. Unlike Lamarre et al,[11] we did not find a difference in age between

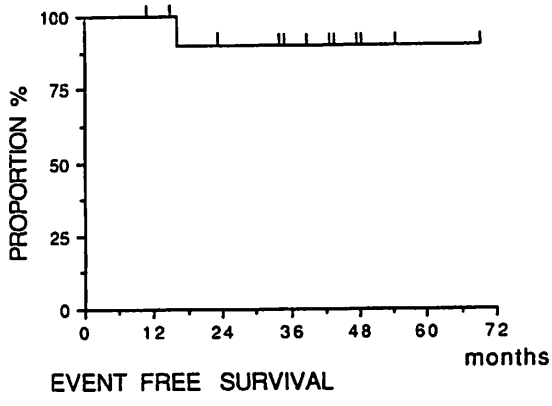

Fig 2. Event-free survival of 13 patients with mediastinal large-B-cell lymphoma who did not receive previous chemotherapy and were treated with aggressive regimens.

males and females, possibly because in their series also patients with immunoblastic lymphoma without evidence of sclerosis were included. These patients were males and characterized by an older age.

Second, the involvement of superficial lymph nodes at presentation is absent in almost all the cases. This fact implies that aggressive surgical procedures such as thoracotomy or mediastinoscopy are often necessary to obtain a diagnosis in these patients. Moreover, the presence of SVCS at presentation has been found in 50% of these patients and is related to the frequent presence of bulky mediastinal disease (76%). Both these findings are reported also by Jacobson et al.[12]

Third, when the disease is advanced, it often infiltrates the kidney (Table 1), which is a site rarely involved in adult NHL. The kidneys, too, are often involved at relapse. Also the involvement of the adrenal cortex was observed. It is very difficult to make hypotheses about this selective tropism to kidneys and the adrenal cortex. On the other hand, bone marrow involvement has never been detected, even in advanced stages. Similarly, CNS involvement was never seen at diagnosis, and it subsequently appeared only in two patients.

Fourth, the disease is characterized by a very aggressive course and a poor prognosis when treated with conventional chemotherapy as described by others.[6,7,10] As opposed to a recent observation,[12] CHOP never produced a CR in our experience, in spite of the use of full dosages of chemotherapy. This finding stresses the inadequacy of the CHOP regimen in the treatment of aggressive lymphoma. As a consequence of these poor results, in recent years we used an intensive chemotherapeutic approach, based on regimens characterized by multiple drugs, given at high dosages and delivered in a short period of time with short intervals between cycles. The MACOP-B was the regimen most frequently used.[13,14]

The results obtained with this approach were encouraging, with a CR rate exceeding 85% and disease-free survival in the complete responders of 90% at 36 months.

These results compare favorably with those currently obtained in all heavily treated aggressive lymphomas. CR was, in fact, obtained in about 70% of patients with aggressive lymphoma treated in our institution with MACOP-B regi-

men during the same period. This favorable outcome is possibly related, at least in part, to the young age of the patients, which enabled us to administer such aggressive chemotherapy regimens at full dosages. Therefore, in our experience, the most important prognostic factor appears to be the type of chemotherapy given. The prognostic relevance of bulky disease, recently stressed by others,[12] was possibly overcome by the use of such aggressive regimens.

After reaching CR, eligible patients received an involved-field radiotherapy on sites of bulky disease (mediastinum). The role of such "consolidation" radiotherapy is difficult to assess. It is noteworthy, however, that consolidation radiotherapy was given mainly in patients with bulky disease (seven of 10) and that the sole observed relapse occurred outside the irradiation field.

Due to the rarity of CNS involvement, CNS prophylaxis seems not to be routinely indicated in this group of lymphomas.

Our observations confirm that the mediastinal large-B-cell lymphoma with sclerosis, a relatively uncommon type of NHL, is also a distinct clinical entity, and suggest that only a very aggressive chemotherapeutic approach is effective for the achievement of CR and possibly the cure of this malignancy.

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