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Original Articles

Preliminary Results of Chemo-Radiotherapy Followed or not by Active Immunotherapy of Stage III and IV Lymphosarcoma and Reticulosarcoma

Correlation of the Results with WHO Categorisation

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Summary. *We treated 101 patients with advanced (stage III and IV) lymphosarcoma and reticulosarcoma at first presentation of the disease or in relapse according to a protocol combining initial chemotherapy, complementary radiotherapy on icebergs, supplementary chemotherapy, and, finally, active immunotherapy.*

The overall complete remission rate was about 79% for lymphosarcoma and 73% for reticulosarcoma. About 50% of the patients were still in remission in each of the two diseases at 2 years; 60% of lymphosarcoma and 44% of reticulosarcoma patients achieved 2-year survival.

This study shows the prognostic value of the WHO classification for lymphosarcoma and reticulosarcoma: the prognosis of prolymphocytic (centrofollicular) lymphosarcoma is far better than that of the lymphoblastic type, which is in turn better than that of the very poor prognosis of the immunoblastic type. The prognosis of reticulosarcoma is intermediate between that of the best-prognosis and that of the poorest-prognosis type of lymphosarcoma.

Introduction

Stage III and IV lymphosarcoma and reticulosarcoma are disseminated diseases that are typical indications for chemotherapy. With vincristine, cyclophosphamide, prednisone, [12], adriamycin [6], bleomycin [4], nitrosoureas [5], VM 26 [15] and/or several other drugs [7], [18] and combinations of drugs [8–10, 21–24], chemotherapy has been shown to be able to induce a high rate of remission and to significantly prolong survival, depending, however, on several factors, the main one being histological classification.

One group [1] has applied Lennert's classification [11]; most others use the classic Rappaport classification [25], which combines several types under the so-called histiocytic type, some of which may have a good prognosis, such as diffuse large-cell prolymphocytic (centrofollicular) lymphosarcoma, some with very poor prognosis, such as immunoblastic lymphosarcoma [16], and a few with intermediate prognosis, such as reticulosarcoma, as shown in this paper.

The present work tests the value of the WHO classification [20], in which tumours of the lymphocytic series are called lymphosarcoma and those of the fixed, so-called mononuclear phagocytes [32] (reticulum cells, dendritic cells etc., which are not in fact macrophages) [29–31], are called reticulosarcoma, and types of lymphosarcomas are distinguished according to the stage of cell differentiation. Hence, among the common varieties the prolymphocytic (centrofollicular), nodular or diffuse type, the lymphoblastic type, and the immunoblastic type are recognised.

A further aim of this paper was to test a strategic design for a protocol comprising an initial chemotherapy, a complementary radiotherapy, a supplementary chemotherapy, and an active systemic immunotherapy, the last being applied to one of two randomised groups of patients. The preliminary results have already been published [21]; they were encouraging and are confirmed by the present evaluation.

Patients and Methods

This therapeutic study concerns a population of 101 patients who received the predetermined protocol mentioned above and described in Figure 1.

The treatment started with a combination of four drugs shown to be active when given singly: adriamycin [6], VM 26 [15], cyclophosphamide [12], and prednisone [12]. Thus, as chemotherapy obeys first-order kinetics [26–28] and as relapses after chemotherapy occur mainly in the sites of larger masses, after 8 months of the chemotherapy described above, we applied localized radiotherapy to the icebergs i.e., to the detectable tumours; then we applied a comple-

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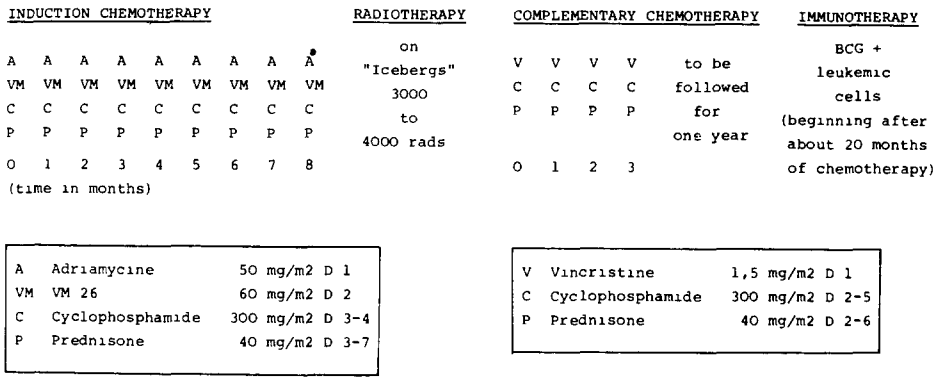

Fig. 1. Scheme of the protocol

Table 1. The patient population

No. of. patients	101
Age	5–70 (Median 43) 10 patients under 15 years
Sex	Female 39 Male 62
Stage III	44
Stage IV	57
Perceptible phase	First presentation 69 Relapse 32
Typing according to WHO Categorisation	
a) Lymphosarcomas	
Prolymphocytic (centrofollicular)	36
Nodular	19
Diffuse	14
Non-determined	3
Lymphoblastic	15
Immunoblastic	18
Unclassified	21
b) Reticulosarcoma	11

Table 2. Stratification of the patients. Correlation between sex, stage, and WHO typing

	Age (Extremes)	Median age	Male	Female	Stage III	Stage IV
Lymphosarcomas						
a) Prolymphocytic (centrofollicular)	19–67	48				
Nodular			13	6	13	6
Diffuse			10	7	5	12
b) Lymphoblastic	3–62	22	10	5	4	11
c) Immunoblastic	3–69	45	10	8	9	9
Reticulosarcoma	15–63	44	6	5	4	7

mentary chemotherapy less intensive than the first, combining vincristine, cyclophosphamide, and prednisone [22], for 12 months. The patients were then randomised to receive or not receive active immunotherapy comprising the application of BCG and the injection of irradiated leukaemic lymphosarcoma cells [13].

This patient population is different from that studied by our Group for the immune markers [2, 3, 14, 17, 19], although some patients were included in both populations. Some of the patients in the present population were not submitted to cell surface marker determination because the biopsy had already been carried out when they were referred to our Service. However, the specimens from all patients included in this study were reviewed at the WHO Reference Center for Neoplasia of Haematopoietic and Lymphoid Tissues [20].

The distribution of the population according to age, sex, stage, perceptible phase of the disease (first presentation or relapse), and the WHO typing is given in Table 1. The correlation between the WHO typing, sex, and stage is given in Table 2.

The present results are still preliminary, since the effect of immunotherapy has not been evaluated. However, the data already collected enables the correlation of results with the categorisation of the WHO Reference Center for the Classification of Neoplasias of Hematopoietic and Lymphoid Tissues [20].

Results

Tolerance

Tolerance was generally good. There were no deaths that could be related to the treatment. Alopecia was the most frequent side effect. Leucopenia at the end of at least one interval and severe enough to slightly delay the next cycle was observed in 41% of the patients. It was complicated by regressive infections in six patients (Table 3).

Overall Remission: Lymphosarcoma (LS) versus Reticulosarcoma (RS)

The incidence of complete remission was 79% (71/90) and that of partial remission 9% for lymphosarcomas

Table 3. Tolerance

Alopecia	85%
Leucopenia < 1500 WVC	41%
Thrombocytopenia < 50.00 Platelets	12%
Regressive infection	6 patients
Moderate nausea	6 patients
Heart failure	1 patient
Asthenia	0
Severe diabetes	1 patient
Haemorrhagic cystitis	1 patient
Acute intolerance to VM 26	3 patients
Renale failure	1 patient
Death due to the treatment	0

(Table 4). It was not much different for reticulosarcoma (8/11 = 73%).

Overall Duration of Remission and Survival: Lymphosarcoma versus Reticulosarcoma

The cumulative curves of remission established according to the direct method are shown for stages III and IV lymphosarcoma and reticulosarcoma in Figure 2. The median is about 2 years for the three categories of patients. There is no significant difference between the three curves, which tend to flatten after about 16 months. Neither is there a significant difference between

Table 4. Therapeutic responses

	Number of patients	Complete remission	Partial remission	Failure
Lymphosarcomas				
a) Prolymphocytic (centrofollicular)	36	31	2	3
Nodular	19	19	0	0
Diffuse	14	9	2	3
b) Lymphoblastic	15	15	0	0
c) Immunoblastic	18	12	2	4
d) Unclassified	2113	4	4	
Reticulosarcoma	11	8	1	2
Total	101	79 (78%)	9 (9%)	13 (13%)

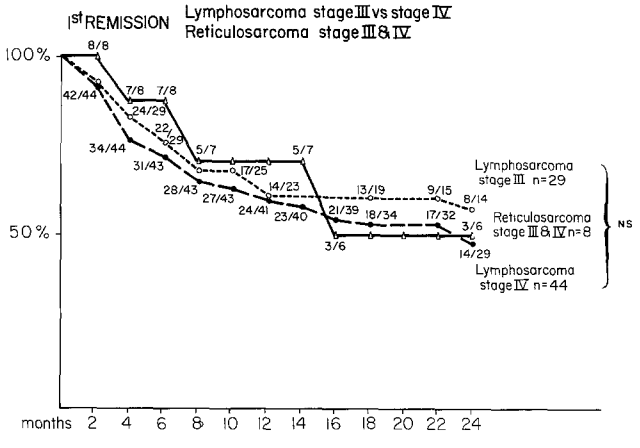

Fig. 2. Direct curves for cumulative duration of first remission in all lymphosarcoma and reticulosarcoma patients

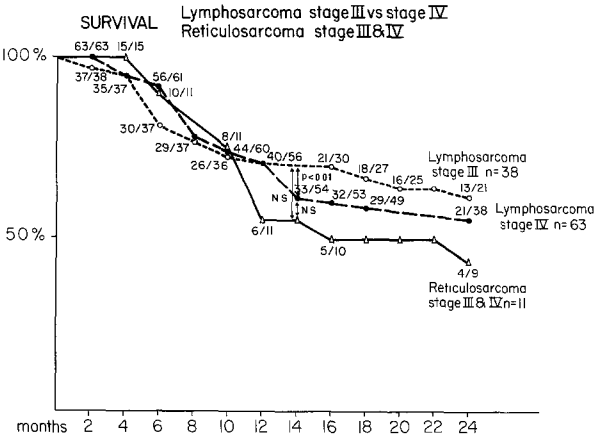

Fig. 3. Direct curves for cumulative duration of survival in all lymphosarcoma and reticulosarcoma patients

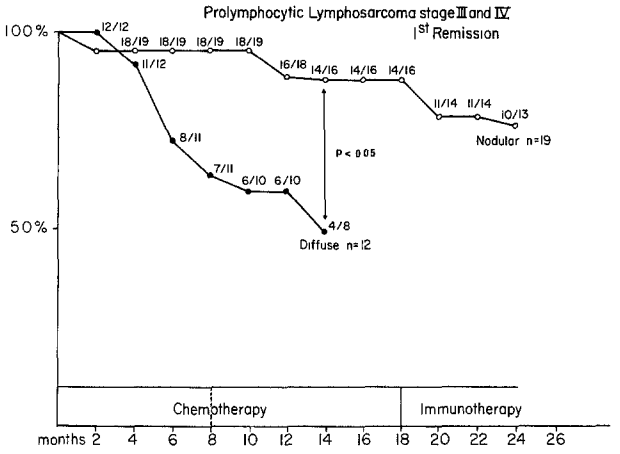

Fig. 4. Comparative duration of first remission in nodular and diffuse prolymphocytic (centrofollicular) lymphosarcoma patients

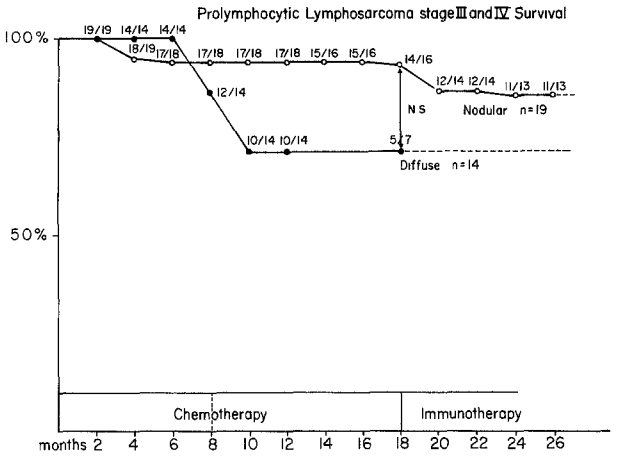

Fig. 5. Comparative duration of survival in nodular and diffuse prolymphocytic (centrofollicular) lymphosarcoma patients

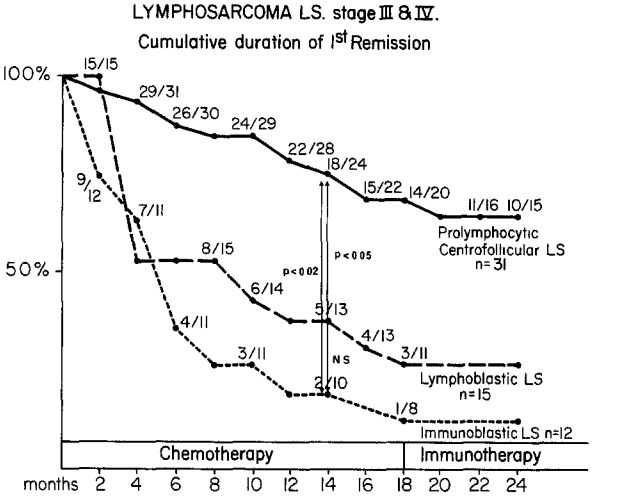

Fig. 6. Cumulative duration of first remission in lymphosarcoma patients according to WHO histocytological typing

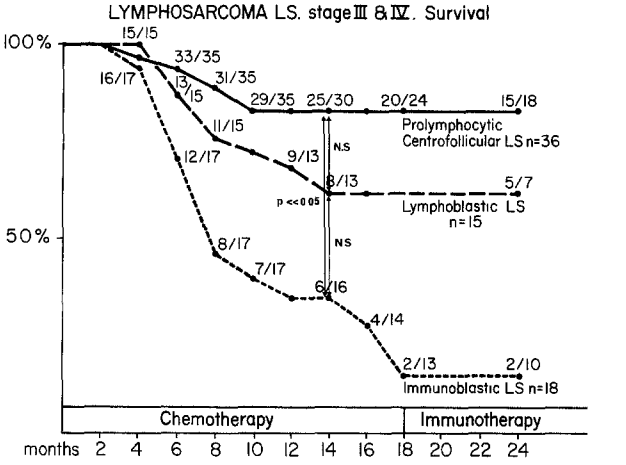

Fig. 7. Cumulative duration of survival in lymphosarcoma patients according to WHO histocytological typing

the cumulative survival curves of stage III and stage IV lymphosarcoma and reticulosarcoma patients (Fig. 3). However, the median survival of lymphosarcoma patients was still not attained at 2 years, while that of reticulosarcoma patients was reached at 16 months.

Remission Induction According to WHO Histocytological Types of Lymphosarcoma

Complete remission was obtained in 31 patients out of 35 with prolymphocytic (centrofollicular) lymphosarcoma (19 out of 19 with nodular and 9 out of 14 with diffuse), in 15 out of 15 lymphoblastic cases, and in 12 out of 18 patients with immunoblastic lymphosarcomas.

Remission and Survival Duration According to WHO Histocytological Types of Lymphosarcoma

Firstly, it can be seen that the remission duration curve is significantly higher for the nodular prolymphocytic (centrofollicular) form (88% at 18 months, median not reached), than for the diffuse prolymphocytic (centrofollicular) form (median at 14 months) ($P < 0.05$) (Fig. 4). The survival curves of these two forms also differ, but the difference is not significant (Fig. 5).

The second observation concerns the differences between the three WHO types of lymphosarcoma: the prolymphocytic (centrofollicular), the lymphoblastic, and the immunoblastic types. The remission curve is much more favourable for the prolymphocytic (centrofollicular) type than for the lymphoblastic type (the difference

is significant, $P = 0.025$); the latter curve appears a little more favourable than that for the immunoblastic type, although the difference between these two types is not significant (Fig. 6).

The same phenomenon is valid for the survival curves: that for the prolymphocytic type is more favourable than that for the lymphoblastic (the difference is highly significant, $P < 0.025$), which seems more favourable than that for the immunoblastic type, though this difference is not significant (Fig. 7).

The results obtained in the cases of reticulosarcoma (Figs. 2 and 3) are intermediate between those for the best and the poorest prognostic types of lymphosarcoma, i.e., similar to those obtained in the lymphoblastic type. This demonstrates the practical importance of distinguishing immunoblastic lymphosarcoma from reticulosarcoma, as the WHO Reference Center does [16].

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