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Diagnostics and therapy of non-Hodgkin lymphomas in childhood

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Many changes have taken place in the diagnosis and treatment of non-Hodgkin-lymphomas in childhood during the last years. From 1979 to 1982, the Working Group for Paediatric Haematology, Oncology and Immunology of the GDR treated 50 children with NHL according to the LSA_2L_2-protocol in a multicentric study. The Kiel-classification was applied for histological diagnosis. Main localizations were the mediastinum and abdomen. The treatment resulted in a complete continuous remission of 65% (Stages I and II: 87%, Stages III and IV: 53%) for all patients, independently of the stage. Patients with extranodal tumours and wide-spread abdominal disease had a very bad prognosis with this protocol.

The non-Hodgkin-lymphomas(NHL) in childhood represent a group of very aggressive diseases differing markedly from NHL in adults. During the last years the results of treatment of childhood NHL have impressively improved. A decisive key for this success was the recognition of the systemic nature of the disease tending to rapid progression originating from apparently localized lesions. This fact forms the rational background of intensive chemotherapy. The combined chemo- and radiotherapy resulted in a considerable progress of long time survival in localized as well as in advanced stages [8, 14, 15].

Our Working Group on Paediatric Haematology, Oncology and Immunology in the GDR was looking for an effective treatment conception for our patients with NHL late in 1977. At that time the best results were published by Wollner et al [15]. Therefore our Working Group decided to adopt the principles of that protocol including some modifications. Here we are going to report on our experience in diagnostics and treatment of NHL during the last years.

Diagnostic measures

All diagnostic examinations in a child suspicious of NHL should be accomplished without any delay. This procedure is outlined in Table I. In general, surgery is confined to lymph node biopsy.

An important exception is NHL with its primary site in the abdominal space representing an absolute indication for laparatomy. In this case diagnostic and therapeutic measures are closely connected. The NHL lo-

TABLE I

Staging procedures for NHL

MANDATORY
1. LBC, platelet count, differential count
2. Chest a. p. and lateral X-rays
3. Bone marrow aspirate and biopsy
4. Lumbar puncture with CSF cytocentrifuged
5. Liver function tests
6. BUN and creatinine
7. Uric acid level
OPTIONAL (depending on clinical circumstances)
1. Bone scan ± skeletal survey
2. Intravenous urogram
3. Contrast studies of Gl tract
4. Myelography
5. Tomography and/or CT
6. Lymphangiography
7. Serum electrolyte levels

calized in terminal ileum and coecum with or without lymph nodes should completely be resected. More often a widespread disease is found in the abdomen permitting just a biopsy. During each abdominal exploration it is necessary to take biopsies from liver and regional and para-aortal lymph nodes. There is no indication for spelenectomy. Moreover, diagnostic laparatomy is indicated exclusively in NHL with primary abdominal site.

STAGING

At present there is no conformity in staging [8, 14]. We prefer the staging according to Murphy [8].

Stage I:

One single site (nodal or extranodal without regional metastases) except mediastinal, abdominal and epidural sites.

Stage II:

Several sites at the same side of the diaphragm; localized gastrointestinal tumours with or without regional lymph nodes.
The following additional staging is applied for B-NHL in stage II:
Stage II-R ("resectable"): Tumour completely resected by surgery.
Stage II-NR ("non-resectable"): Tumour not completely resected.

Stage III:

Tumour localized on both sides of the diaphragm, all widespread abdominal manifestations (thymus, lymph nodes, pleura), epidural sites.

Stage IV:

ALL NHL with unequivocal disease in the bone marrow and/or CNS

Histological classification

Nowadays there exist several international classifications of lymphoma [1, 4, 6, 10, 12]. We preferred the Kiel-classification initiated by Lennert et al and recommended by the European Lymphoma Club [2].

Immunological classification

By means of specific antisera and the sheep red blood cell rosetting test, lymphoma cells and non-T-non--B-cell lymphomas were classified according to the respective cell surface marker. Moreover, in a certain proportion on non-T-non-B-cell lymphomas there is evidence of the common acute lymphatic leukaemia antigen (cALL) on cell surfaces.

Multicentric treatment study LSA_2L_2

Patients. In 1977–1982 the Working Group on Paediatric Haematology, Oncology and Immunology of the GDR* treated 50 children (15 girls and 35 boys with a mean age of 8 years and 10 months) by means of the LSA_2L_2 protocol. None of the patients had been treated before entering the study.

Localization and staging. For primary localization of the tumours, see Table II. In 35 out of 50 patients (about 70%) the primary site was in the abdomen or mediastinum. Five patients showed bone marrow involvement with a blast proportion of less than 25% at the time of diagnosis. (A bone marrow involvement with more than 25% blasts was classified as ALL and not admitted to this study).

Staging took place according to the criteria of Murphy and Hustu [8]. Abdominal tumours were treated surgically attempting complete resection in 8 patients. In 9 children the abdominal disease was so advanced that a diagnostic biopsy was only possible.

Histological classification. Histologic examinations were carried out at the local Institutes of Pathology of the respective centres. The diagnosis of NHL was the criterion of admission to the study. In most of the cases the biopsy specimens could be re-eval-

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TABLE II

NHL therapy study LSA_2L_2 (1977–1982) 30/6/82

Primary sites	No. n	PTS per cent	Stages			
			I	II	III	IV
Intra-abdominal	17	34	—	8	9	—
Mediastinal	18	36	—	—	15	3
Peripheral nodal	6	12	1	1	2	2
Nasopharyngeal	4	8	1	3	—	—
Extranodal	5	10	2	1	2	—
Total	50	100	4	13	28	5
			8	26	56	10

uated by one of the authors (D. Katenkamp) (see Table III). In 9 patients no re-evaluation was possible, these cases were classified as lymphoblastic lymphoma (histologic diagnosis by the local pathologist).

Therapy. The therapeutic procedure was derived from the protocol recommended by Wollner et al [14] (Fig. 1).

Surgery. In addition to the abovementioned principles in cases of abdominal tumours too extensive at the time of diagnosis we aimed at a second look laparotomy at about three weeks after starting combined chemoradiotherapy in order completely to excise rest tumours.

Radiation. 20 Gy were applied to the primary lesion. In the cases of widespread intraabdominal disease the same dose was applied to the entire abdominal cavity.

CNS prophylaxis. Intrathecal methotrexate was given to all children. Moreover, 20 patients had an irradiation of the skull (18 Gy) and 11 patients intrathecal colloidal radiogold (^{198} Au). There was no case of initial CNS disease.

TABLE III

NHL therapy study LSA_2L_2 (1977–1982) 30/6/82

Histological classification	No. PTS	
	n	pe cent
Lymphoblastic lyphoma		
Unclassified	23	46
Burkitt type	7	14
Convoluted cell type	8	16
Immunoblastic lymphoma	3	6
Not classified	9	18

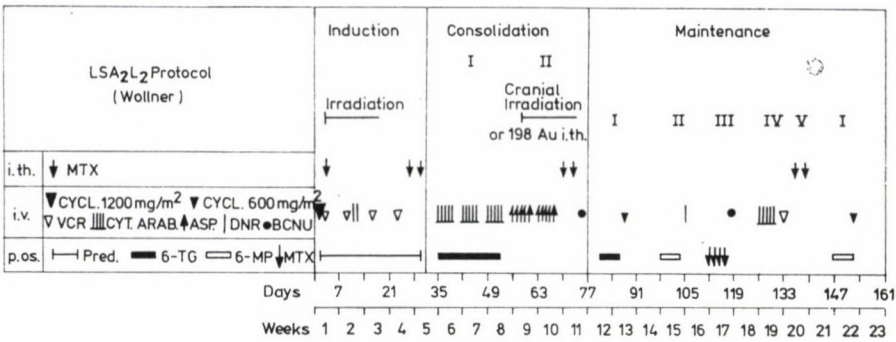

FIG. 1. Treatment protocol LSA_2L_2 used for children with NHL

Chemotherapy. Chemotherapy represents the most important component of this treatment protocol (for details see Fig. 1).

Statistics. Complete remission means that there was no detectable disease. For the calculation of remission rates we applied life table analysis according to Kaplan and Meier [3].

RESULTS

Of the 50 children 44 (88%) achieved complete remission (Table IV). In all patients this was accom-

TABLE IV

NHL therapy study LSA_2L_2 (1977–1982)

Results of Therapy	30/6/82	
	n	per cent
Number of patients	50	100
Deaths in initial stage	6	12
Complete remission	49	88
Remission deaths	2	4
Relapses, total	7	14
Bone marrow	1	2
CNS	3	6
BM/CNk	1	2
Others	2	4
In 1st CCR	35	70
Median 1st CCR time	18	Months
Off therapy	17	34
Relapses off therapy	1	2

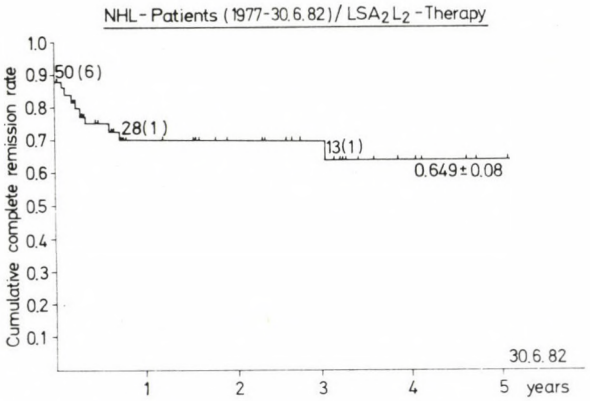

FIG. 2. Calculated continuous complete remission (CCR) for all patients by means of life-table-analysis according to Kaplan and Meier [3]

plished after the induction period. Six patients were non-responders with primary localization of lymphomas in abdomen (3), mediastinum (2), and extranodal (1).

Figure 2 presents the cumulative complete remission rate of all patients. From this graph it can be seen that with one exception, all relapses occurred during the first nine months of treatment. There were altogether 7 relapses: bone marrow (1), CNS (3), bone marrow and CNS (1). Two patients suffered from local relapses in the abdomen and mediastinum, respectively. Two children died of infection during remission; for statistical purposes they were classified as relapses.

At present, 35 out of 50 patients are still in continuous complete remission. The mean duration of remission was 18 months. In 17 children, treatment was already terminated. Up to now there has been a single relapse after the termination of therapy. As it can be seen from Fig. 2, the remission was complete in 65% of the patients after five years. The rate of complete remission in proportion to the stage of disease is presented in Fig. 3. Patients classified as stage I and II may expect a rate of 87% as contrasted with a CCR-rate of 53% in stage III and IV patients.

From Fig. 3 it can also be concluded that the prognosis of localized resectable abdominal NHL was good, quite in contrast to wide-spread abdominal disease (Stage III). The five patients with bone marrow involvement (Stage IV) are still free of relapses.

The course of disease in relation to the initial tumour localization is shown in Fig. 4. The prognosis is extremely bad for patients with extranodal and extensive abdominal disease in contrast to lymphomas localized in lymph nodes, mediastinum and Waldeyer's tonsillar ring.

Of 17 patients with abdominal lymphoma 3 were non-responders. Out of this group 4 relapsed very

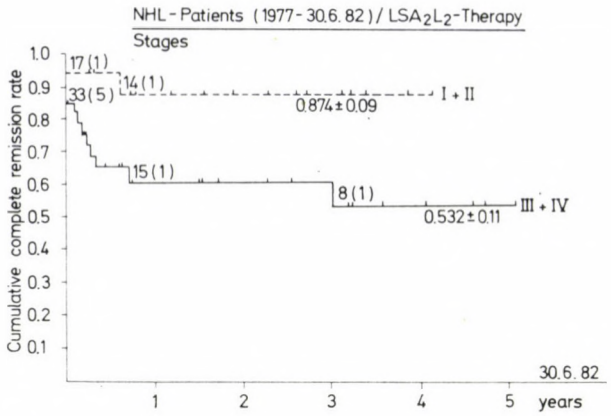

FIG. 3. Influence of the stage of disease on CCR-rate

early during treatment and the above-mentioned patient who relapsed after the termination of therapy suffered from initial abdominal Burkitt type NHL.

Figure 5 shows the results of treatment in relation to the histological diagnosis. Nine patients have not been included owing to insufficient classification.

DISCUSSION

The following conclusions may be drawn from the results of this multicentric LSA_2L_2-study.

1. Patients with NHL stages I and II have a 87% prognostic chance of CCR after four years independently of histology and localization.

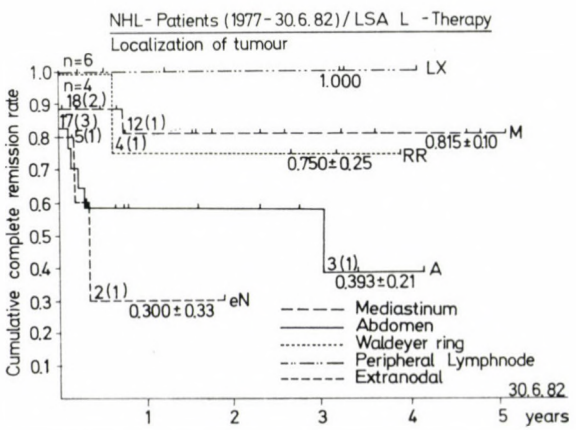

FIG. 4. Influence of primary localization of lymphomas on CCR-rate

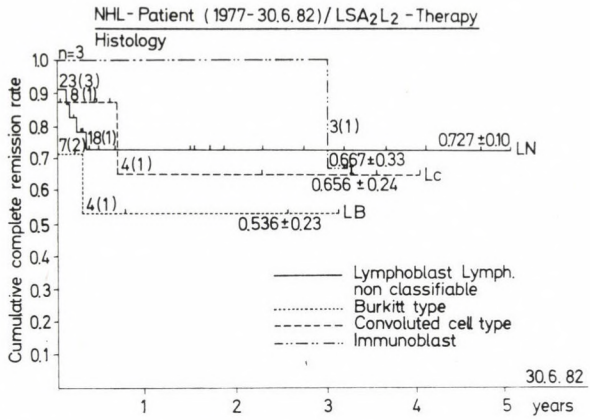

FIG. 5. Influence of histological classification on CCR-rate

2. Patients with stages III and IV have a prognosis of 53% CCR after five years.

3. Extended and non-resectable abdominal involvement (stage III) with NHL of Burkitt-type corresponding to immunologic B-type lymphomas still implies a gloomy prognosis. Notwithstanding a temporary remission all these patients die in relapse.

4. All patients with stage II and abdominal localization live in CCR after 48 months. This clearly points to the critical importance of complete resection in this group.

5. Almost all relapses occurred during the first year of treatment irrespective of the clinical stage and histology.

6. Bone marrow involvement implies no poor prognosis as all these patients survived in the first CCR.

Thus the LSA_2L_2-protocol resulted in a distinct improvement of prognosis as compared to previous reports on the treatment of childhood NHL [11, 16]. Even though the results of our multicentric study do not permit a strict comparison with results of other groups, a synopsis of recent results revealed the same trend (Table V).

The rates of complete remission in stages I and II have attained a range challenging a future refinement of therapy of these children. The hitherto existing protocol was likewise aggressive for all patients with NHL irrespective of stage, localization and histology. Our results indicate that in stage I and II patients a less aggressive protocol might result in the same survival rates with less side effects. The same conclusion might be true for patients with completely resectable abdominal lymphomas.

In children with widespread intraabdominal NHL the LSA_2L_2 protocol resulted in complete failure. This holds true for other protocols, too [9]. For this reason several centres are looking for new therapeutic regimes for this group of patients, with e. g. cyclophosphamide, intermediate dose

TABLE V

2 years surrival in children with NHL. Treatment results during the last 20 years

Year of study	Number of patients	Stages I–IV 2 years survival percent	Authors
1962–1973	64	30	Pinkel et al 1975 (13)
1960–1970	31	32	Murphy et al 1977 (8)
1964–1971	43	11	Wollner et al 1976 (16)
1971–1976	39	73	Wollner et al 1979 (17)
1975–1978	69	55	Murphy et al 1980 (9)
1976–1980	26	54	Pichler et al 1981 (12)
1976–1980	111	62	Müller – Weihrich et al 1981 (10)
1977–1982	50	65	Zintl et al 1982 (18)

MTX and VM [13] playing an important part.

The role of radiotherapy cannot finally be evaluated. From the historical point of view radiotherapy meant a progress in the treatment of NHL. It is generally accepted that a small percentage of children with localized NHL may be cured by radiation. Nevertheless, this is not valid for the majority of patients and real improvement of the therapy was only realized by the introduction of intensive polychemotherapy. Thus a high percentage of mediastinal NHL may be cured by chemotherapy only.

At present therapeutic endeavours aiming at an improvement of cure rates for advanced disease, too, are centred mostly on B-cell lymphomas.

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