Hodgkin’s Lymphoma — Prognosis as Related to Histology, Clinical Stage and Treatment

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The rapid advances in modern chemotherapy and actinotherapy of Hodgkin’s lymphoma and an improvement in its diagnosis have ushered in numerous novel procedures. This is a preliminary analysis of the results of treatment of 117 patients with actinotherapy, polychemotherapy, consisting of a chemotherapeutic four-combination as substitution for MOPP and a combined actino-chemotherapy. Actinotherapy was found more efficient in localized disorders of stages I and II, while polychemotherapy proved the more suitable when the disease was generalized — stages III and IV. The analysis of our results has brought only partial support to the prognostic significance of the histological classification of Hodgkin’s lymphoma according to Rye. No difference of statistical significance has been noted between the histological types of lymphocyte dominance, nodular sclerosis and mixed cellularity. Lymphocyte depletion alone showed a conspicuously worse prognosis than the other histological types.

Key words: Hodgkin’s lymphoma, treatment results, chemotherapy, actinotherapy, combined therapy.

During the past decade an extraordinary attention has been devoted to a classification of Hodgkin’s lymphoma (H. L.), account being taken of the prognosis of the various types capable of being histologically characterized [3, 5, 12], and of the clinical stages of the disease [12, 17]. But the remaining factors bearing on H. L. patients’ survival, such as sex, age, the time lapse since the last remission etc., have also been intensively studied [8, 11, 12, 17].

Simultaneously with the development of megavolt actinotherapy and synthesizing of new chemotherapeutic drugs, several schemes have been worked out for the treatment of H. L. in various clinical stages [1, 7, 12]. Since 1968 consistent efforts have been made to apply these new therapeutic concepts also at the Oncological Institute in Brno. The present paper is meant to bring a preliminary evaluation of our diagnostic results, i.e. a determination of the clinical stage and the histological type in accordance with the results of world statistics, and in addition, to assess the effectiveness of the various therapeutic procedures applied at this Institute.

Material and Methods

1. Selection of patients. During the period 1968—1972 a total of 117 newly registered patients with a histologically verified diagnosis of H. L. were treated at
our Institute, 56% of them were men and 44% women. The age distribution of the patients is shown in Fig. 1. From this number 44 patients, i.e. 37.6% died by the third year since the onset of the disease. The extent of the disorder in our group has been evaluated by means of the Stanford classification of H. I. from the year 1970. The percentage representation of the various clinical stages was as follows: stage I — 28.0%, stage II — 36.4%, stage III — 20.3%, stage IV — 15.3%. Because of the small number of patients involved here, only stages I—IV are used, without subdivisions a, b, as such subgroups would prevent an evaluation of the entire set. The histological evaluation has been made according to the Rye classification [14].

2. Treatment. The patients were assigned to the therapeutic scheme in accordance with the clinical stage of their disorder and this scheme was adhered to consistently insofar as the patient’s clinical state allowed it. The first scheme consisted of a radiotherapy administration of 4000 rad given intratumorously. The source was $^{60}$Co for local irradiation, though predominantly applied by the method of extend field irradiation and in some cases by that of mantle irradiation. This scheme was applied to patients in the clinical stages I, II and IIIa. Exceptionally, simple acti-notherapy alone was also used in stages IIIb and IV, in a total of 12 patients only, predominantly of advanced age, in a poor clinical state, in whom chemotherapy would constitute a rather radical overall intervention. The second scheme was that
Table 1. Scheme of chemotherapeutic treatment

<table>
<thead>
<tr>
<th>Substance</th>
<th>Day</th>
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<tr>
<td></td>
<td>1</td>
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<tr>
<td>CFA 650 mg/m²</td>
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<tr>
<td>Velbe 10 mg i. v.</td>
<td></td>
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<tr>
<td>Natulan 10 mg/m² per os</td>
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<tr>
<td>Prednison 40 mg per os</td>
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CFA — Cyclophosphamide i. v. in short-term infusion. Prednisone was administered in 1st and 4th series and the Table gives the dose per patients per day. The series is repeated 6x with a 3—4-week interval, counted from the 14th day of the preceding series.

of polychemotherapy with a cytostatic four-combination substituting for MOPP [4, 6]. At the start of the regimen, TS 160 was applied instead of the original Mechloretamine; however, it proved highly toxic and was eventually replaced by Cyclophosphamide. Oncovine in the original MOPP is replaced by Velbe. The scheme of our chemotherapeutic regimen is shown in Table 1 and was applied to patients in the clinical stages IIIb and IV. The third scheme, applied predominantly in patients with a generalized disease, or following an early relapse after actinotherapy, or with residual findings after chemotherapy, consisted of a combination of our routine actinotherapy and our chemotherapy. Hence, our third therapeutic scheme was made use of following a partial or total failure of the first or second scheme.

3. Statistical analysis. Because of the rather short-term follow-up period of our patients, we have not used the currently employed evaluation of prognosis, nor of the success of the therapy expressed by a five-year survival rate, eventually by a long-term total remission. Instead, we utilized the analysis of a three-year survival rate in the various patient groups from the time the diagnosis had been established. Patients' resistance to tumor and also the effectiveness of the therapeutic intervention is assessed by means of a resistance index integrating the percentage of surviving patients and length of their survival [15]. All the three formulae needed for a calculation of the resistance index remain valid for clinical requirements. Only when transferring the time of death of individual patients is $d \times x$, equal to the follow-up period of the group, fitted to the relative number (in our case 36 months). Then all patients surviving beyond 36 months have a resistance index $R = 1.00$. The resistance index of a group of patients then may be compared with the corresponding period of another group and the intergroup difference may be evaluated by means of the nonparametric median test.

Results

1. Distribution pattern of various histological types and prognosis related to histological types of H. l. In our set of patients the lymphocyte predominating (LP)
type was represented in 26% of the cases, the nodular sclerotic (NS) type in 14.2%, the type of mixed cellularity (MC) in 45.6% and the type of lymphocyte depletion (LD) in 14.22% of cases. The distribution pattern of the various histological types of H. I. according to patients' age and sex is shown in Fig. 2. The most favorable prognosis in our mode of treatment was with the histological type LP with a resistance index of 0.928. Somewhat less favorable as regards prognosis were the histological types MC with a resistance index of 0.908, and NS with index 0.895. No difference of statistical significance was found between these two histological types. The type with the least favorable prognosis proved to be that of LD — index 0.843. Resistance in these patients, measured by the survival rate in dependence on time from the onset of the disease is significantly lower than that in patients with the remaining histological types ($p < 0.05$) (Fig. 3).

2. Prognosis in dependence on the clinical stage of H. I. An analysis of these data permits us to conclude that the clinical stage of the disease plays an essential role in the prognosis of H. I (Fig. 4). As already stated, because of the small number of patients in the various clinical stages, no further subdivision was made into subgroups a. b. The best prognosis was shown by the clinical stage I with a resistance index 0.890, then follow stage II — index 0.812 and stage III — index 0.864. The least favorable prognosis was in the case of generalized disease in stage IV with a resistance index of only 0.734. No differences of statistical significance have been found in our group between clinical stages I, II and III, while stage IV differs significantly from all the previous three ($p < 0.01$).

3. Effectiveness of the various therapeutic procedures. A study of these procedures for the whole group regardless of the clinical stage of the disease or the histological type revealed that statistically identical therapeutic results were yielded by actinotherapy with a resistance index of 0.883 and by polychemotherapy with a resistance index of 0.851 (Fig. 5). Inferior results were obtained in a group of 62 patients treated with a combined actino- and chemotherapy index 0.788. This figure is significantly different from that of a group of patients treated with actinotherapy alone ($p < 0.05$), but statistically concordant with that of a group treated only with polychemotherapy.
More interesting results came to light from a comparison of the effectiveness of the various therapeutic modes in dependence on the clinical stage of the disease (Fig. 5). In treating localized disease of stage I and II regardless of its histological type, use was made of actinotherapy, or of actinotherapy in combination with the usual polychemotherapy, which in this group was applied until relapse occurred, and when H. I. progressed into further stages. For the first and second stage, actinotherapy — resistance index 0.914 — proved to be more effective than in combination with polychemotherapy — resistance index 0.793. The differences in resistance of the two groups of patients are of statistical significance \((p < 0.05)\). In the clinical stages III and IV use was made of all the three therapeutic schemes. Here, treatment with actinotherapy alone (index 0.792) and with combined actinochemotherapy (index 0.800) proved to be equally effective. Very slightly improved results were achieved with simple polychemotherapy — resistance index 0.829. All the therapeutic results in clinical stages III and IV are statistically identical.

**Discussion**

The most frequently represented histological type in our group was the MC type, which is in agreement with the majority of results published thus far, as revie-
Fig. 5. Results of treatment of H. l. A — actinotherapy. Ch — polychemotherapy. C — combined actinotherapy. Figures within columns (see Fig. 3).

Wed by Braylan [2]. The remaining histological types are fairly evenly distributed, similarly as in Lukes's numerous group [13]. A deteriorating prognosis was found in the successive histological types from LP through MC to LD, which again agrees with literary reports referred to above [3, 5, 10, 12]. A slightly worse prognosis, without statistical significance, was shown in our group by the histological type NS, which ranged between MC and LD. This fact, by which our group differs from all the relevant literary reports may be due to the relatively small numbers of patients of the NS type in our study. Another reason for the inferior prognosis in the NS type lies in the less radical actinotherapy in this otherwise prognostically favorable type. This less radical actinotherapy in our patients actually consisted in a simple local irradiation, maximally in extend field therapy, but no mantle irradiation mode has been used as in the histological types MC and LD.

Our results have confirmed the prognostic significance of the various clinical stages according to the Stanford classification. Probably because of the short-term follow-up of our patients — 36 months — no differences of statistical significance have been found between the various clinical stages, but only between stage IV and the rest. A similar survival pattern during the first three years of the disease is also evident from reports previously published [10].

As to the effectiveness of the various modes of treatment, actinotherapy and polychemotherapy have been found to be roughly equally effective. Lower results were achieved through a combination of actino- and chemotherapy. A plausible explanation of this might be that the combined therapy is for the most part applied to patients with short-term or incomplete remission, or to those reacting toxically
to the treatment — hence, generally patients in an unsatisfactory state. The striking successes of a combined radical actinotherapy and polychemotherapy reported by Kaplan’s group [12] are probably due to the use of a maximum possible therapy right from the initiation of treatment in the majority of the patients.

When the various therapeutic schemes in our study are compared for their effectiveness on localized disease of stages I and II, actinotherapy alone proved more suitable than in combination with polychemotherapy. This contradiction with works reporting a higher effectiveness of the combined therapy also in localized H. 1. [16] is taken to stem from the relatively restricted number of patients in the relevant study and our present group, and also from the fact that we always had recourse to chemotherapy in these stages only when the disease had progressed further despite a preceding local irradiation treatment. In stages III and IV, we applied all the three therapeutic schemes. Here, as in literary reports [9, 12], polychemotherapy proved the most effective.

The results of treatment in our group of patients may be summarized in the sense that the concept of a predominant actinotherapy in stages I and II of Hodgkin’s lymphoma and a predominant chemotherapy in stages III and IV has proved effective. A more radical primary approach seems necessary in future to each patient, particularly in stages III and IV, where beneficial results were achieved by Kaplan [12]. It will be especially important in future to introduce a more radical treatment consisting principally in mantle irradiation in patients with the histological type NS. In addition, a more extensive combination of radical actinotherapy with chemotherapy might be considered right from the onset of the disease, at least in some patients of stages I and II.

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References


