The balance between cure and late effects in childhood Hodgkin’s lymphoma: The experience of the German-Austrian Study-Group since 1978

An overview

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Summary

Background: For more than 20 years now treatment strategies geared to the specific problems in children with Hodgkin’s disease (HD) have been tested by different pediatric oncologic groups. In these approaches high priority was given to the reduction of late effects caused by radio- and chemotherapy, next to the goal of achieving high survival rates. Combined modality treatment as a standard option has enabled reduced dosages and fields of radiotherapy and lowered cumulative total doses of critical cytotoxic agents.

Methods: In Germany and Austria more than 1,200 children and adolescents with HD have been treated in 5 consecutive multicenter studies since 1978. The main general objectives were to determine the extent to which radio- and chemotherapy can be reduced within a combined treatment concept and to find an effective chemotherapy (CT) of low long-term toxicity. Nitrogen-mustard in MOPP was replaced by adriamycin (OPPA) in the first 2 cycles of CT and by cyclophosphamide (COPP) in the additional cycles. The total number of cycles was reduced for early and intermediate stages. From the second study (HD-82) onward, patients were allocated to 3 treatment groups (2, 4, or 6 cycles, respectively) according to disease stage, and involved-field irradiation (IFI) was given instead of extended-field irradiation (EFI).

Results: In study HD-82 standard doses of IFI in the 3 treatment groups (TG) after 2, 4, or 6 cycles of CT were 35, 30, or 25 Gy. In a total of 203 patients probabilities for event-free survival (pEFS) and survival (pSV) were 95% and 93% at 13 years. In the 3 TG pEFS was 97%, 92% and 85%. In an international study (SIOP-HD IV-87) 65 stage IV patients were treated according to the TG 3 schedule of HD-82 (2 OPPA, 4 COPP, 20 Gy IFI). After 7 years pEFS is 77% and pSV 93%. Late effects of OPPA, respectively, OPPA/COPP: The cumulative risk for secondary leukemias after 10 years is 0.5% for all patients and 0.3% for those who remained in first remission. Cardiomyopathies have not been observed (cumulative total dose of adriamycin 160 mg/m²).

Increased FSH-levels indicating impaired spermatogenesis were found in 40% of the male patients without relapse. The frequency was related to the number of procarbazine containing cycles (29% after 2 cycles, 46% after 4, and 63% after 6). In study HD-90, procarbazine in OPPA was replaced by etoposide (OEPA) for the boys (cumulative dose 1.000 mg/m²), whereas girls received OPPA again. In TG 2 and 3, both boys and girls received COPP. Standard doses of IFI were reduced to 25, 25, and 20 Gy. The preliminary evaluation after nearly 5 years reveals that the reduction of radiation doses did not impair the results after OPPA and OPPA/COPP. In localized stages 2 OEPA (boys) and 2 OPPA (girls) produced the same results. In the 15-18 years age group compared to the younger patients identical values for pEFS were achieved.

Conclusions: The ratio between cure rates and late effects has been favourably balanced with OPPA, respectively, OPPA/COPP plus low-dose IFI, especially in female patients. In boys the risk of testicular dysfunction can be further reduced by substituting OEPA for OPPA. Age up to 18 years does not appear to be of any significance for the treatment results with our therapy concept.

Key words: gonadal dysfunction after chemotherapy, late effects of chemotherapy, OEPA, OPA, OPPA, treatment of Hodgkin’s disease in children

Introduction

More than 20-years ago Kaplan and Donaldson from Stanford initiated a special treatment approach for children with Hodgkin’s disease (HD), in an attempt to reduce the late effects of high-dose extended-field irradiation [11, 20]. They combined low-dose extended-field irradiation with 6 cycles of MOPP chemotherapy for all stages. Subsequently, more and more pediatric oncologic groups in different countries started to test treatment strategies geared to the specific problems in children, moving away from the established concepts for adult patients [3, 6, 17, 18, 23, 25-34]. In these studies, high priority was given to the reduction of late effects of radio- and chemotherapy, next to the goal of achieving high survival rates. Combination of the two treatment modalities as a standard option proved to be the only possible route to replace high-dose extended-field by low dose involved-field irradiation and to limit the cumulative total doses of the cytotoxic agents to an acceptable level.

The most relevant potential sequelae of high-dose radiotherapy (36–44 Gy) are: Growth impairment of bones and atrophy of soft tissues (in children); com-
The second treatment modality, chemotherapy can also cause severe late effects: After 6 cycles of MOPP [9] persistent azoospermia is found in the majority of male patients, and the cumulative risk of secondary leukemias is 3%-6% (mostly due to nitrogen-mustard) [1, 8, 10, 16, 20, 21, 35]. Six cycles of ABVD are associated with the risk of chronic cardiomyopathy due to the cumulative Adriamycin dose of 300 mg/m² and of impaired lung function due to 120 mg/m² bleomycin (both are comparatively more likely in children) [17, 18, 22]. The frequency and severity of most late effects caused by cytotoxic agents are clearly related to the cumulative total doses of the critical drugs and, to some degree, the combination with radiotherapy [12, 22].

The German-Austrian HD-studies

**General aspects**

In Germany and Austria, children and adolescents with HD have been treated in consecutive multicenter studies since 1978, i.e., for 17 years now [3–7, 25–33]. The general objectives of these studies were and continue to be:

- to determine the extent to which chemo- and radiotherapy can be reduced within the context of a combined modality treatment for all disease stages;
- to find a chemotherapy regimen of high efficacy and low long-term toxicity;
- To reevaluate the relevance of exploratory laparotomy and splenectomy within a combined modality treatment for all disease stages;
- to determine the extent to which chemo- and radiotherapy can be reduced within the context of a combined modality treatment for all disease stages;
- to find a chemotherapy regimen of high efficacy and low long-term toxicity;
- To reevaluate the relevance of exploratory laparotomy and splenectomy within a combined modality treatment for all patients.

Our investigations on limitations of splenectomy and laparotomy have been reported elsewhere [25, 29, 31, 33]. The present contribution will be concerned with the clinical results of these trials.

A total of more than 1,200 patients from 90 centers in Germany and Austria were enrolled in 5 consecutive trials HD-78, HD-82, HD-85, HD-87 and HD-90 [3, 25, 27–29] (Table 1). Survival rates (including all patients of all stages) exceed 90% in all 5 studies reaching and exceeding 95% from the second study (HD-82) onward (Table 1, Figure 1).

When we opened the first trial in 1978 [3, 6] the first reports about secondary leukemias and male sterility after MOPP had already been published. Thus, we decided to modify the chemotherapy as follows:

- nitrogen-mustard was replaced by Adriamycin in the first 2 cycles (OPPA) and by cyclophosphamide in the later cycles (COPP);
- the number of cycles was limited to 2 and 4 for early and intermediate stages.

The 4 Adriamycin applications of the 2 OPPA cycles (Table 2) add up to a total of 160 mg/m² which corresponds to the cumulative dose of 3 ABVD cycles. The dose intensity of vincristine and prednisone is also relatively high: the total cumulative doses of the two drugs are identical with the doses applied in 3 MOPP cycles.

**Study HD-82**

The second study HD-82 [6, 25] introduced the basic scheme of our treatment concept, which has not been changed since. The study was mainly designed to answer the question if the chosen risk-adapted chemotherapy with OPPA and OPPA/COPP enables a considerable reduction of radiotherapy concerning both fields and dosage.

**Table 1.** Five consecutive German/Austrian therapy studies for HD in children and adolescents since 1978: Patient characteristics and probabilities of survival (pSV).

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Boys/girls</th>
<th>Median age (y, m)</th>
<th>pSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD-78</td>
<td>170</td>
<td>109/61</td>
<td>12; 1</td>
<td>91 (16 years)</td>
</tr>
<tr>
<td>HD-82</td>
<td>203</td>
<td>125/78</td>
<td>12; 1</td>
<td>95 (13 years)</td>
</tr>
<tr>
<td>HD-85</td>
<td>98</td>
<td>58/40</td>
<td>12; 10</td>
<td>98 (10 years)</td>
</tr>
<tr>
<td>HD-87</td>
<td>169</td>
<td>126/70</td>
<td>12; 1</td>
<td>96 (8¼ years)</td>
</tr>
<tr>
<td>HD-90</td>
<td>574</td>
<td>317/257</td>
<td>13; 0</td>
<td>99 (4¼ years)</td>
</tr>
<tr>
<td>All</td>
<td>1241</td>
<td>735/506</td>
<td>12; 7</td>
<td>96 (16 years)</td>
</tr>
</tbody>
</table>

**Table 2.** Application and dosage of cytotoxic drugs in one OPPA-cycle.

<table>
<thead>
<tr>
<th>Day</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>1, 15</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1, 8, 15</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>1 to 15</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 to 15</td>
</tr>
</tbody>
</table>

**Figure 1.** Kaplan–Meier curves of survival (pSV) for the total patient groups (all stages) in the 5 German/Austrian multicenter studies for HD.
The patients were allocated to three treatment groups (TG) according to disease stage and received 2, 4, or 6 cycles of chemotherapy, respectively (Figure 2). The complete 2 cycle-regimen of TG 1 and the initial 2 cycles in TG 2 and 3 consisted of OPPA (Table 2). The subsequent 2 or 4 cycles in TG 2 and 3 applied COPP with cyclophosphamide. Radiotherapy was placed at the end of the total treatment period and strictly limited to the initially involved fields. The standard dosage was reduced to 35, 30, and 25 Gy in the 3 TG, depending on the length of chemotherapy.

Results: The probabilities for event-free survival (pEFS) at 13 years in the 3 TG are 97%, 92% and 85%, respectively (Figure 3). In the total group of 203 patients which includes all stages the overall survival (pSV) is 95% (Figure 1) and pEFS 93% at 13 years. We concluded that involved-field irradiation at the applied reduced doses can be successfully used in combination with OPPA/COPP in a risk adapted treatment schedule.

SIOP-study HD-IV-87

In 1987, a European trial for children with stage IV Hodgkin's disease was initiated within the International Society of Pediatric Oncology (SIOP) including the German-Austrian Group [29]. The treatment concept was identical with the one employed in TG 3 of study HD-82, providing 2 cycles of OPPA and 4 cycles of COPP plus involved-field irradiation of only 20 Gy.

Results: After more than 7-years the group of 65 patients with stage IV disease shows a pEFS of 77% and a pSV of 93% (Figure 4). The participating groups in France and Italy documented a significant improvement of their results in stage IV compared to their preceding studies which had employed MOPP and MOPP/ABVD [23, 24].

Late effects of OPPA/COPP

One of our major goals was to identify the most relevant late effects associated with our highly efficacious treatment concept (involving OPPA/COPP chemotherapy plus involved-field irradiation). The incidence of secondary leukemias was evaluated in 686 patients from four studies (HD-89, HD-82, HD-87, HD-90) who had been treated with OPPA/COPP. We found a cumulative risk of secondary leukemias after 10 years of 0.5% for all patients (those with relapses and salvage-therapy included), 0.3% for the patients who remained in first remission, and 4% for those with additional salvage therapy. These risks are much lower than after MOPP in adults and in children [21].

Cardiomyopathies have not been observed in 17 years since OPPA/COPP was introduced. Due to the relatively low total cumulative Adriamycin dose of 160 mg/m², the probability of chronic cardiomyopathies to occur is considered very low.

However, Brämswig and co-workers in cooperative endocrinologic examinations found increased FSH-levels indicating impairment of spermatogenesis in 40% of the treated male patients [5]. The percentage of these abnormal findings was related to the number of procarbazine containing cycles: 29% after 2 cycles, 46% after 4 cycles, and 63% after 6 cycles. In contrast, no dysfunction of the ovaries was seen after OPPA/COPP chemotherapy in girls without pelvic irradiation [4].

Study HD-85

After realizing the gonadotoxic effect of procarbazine in boys, we addressed this problem in the sub-

Figure 2. Therapy scheme of study HD-82.

Figure 3. Kaplan–Meier curves of event-free survival for the 3 treatment groups in study HD-82.

Figure 4. Kaplan–Meier curves of survival and event-free survival for 65 patients (stage IV) in study SIOP-HD IV-87.
sequent studies. In HD-85 we attempted to eliminate procarbazine completely from chemotherapy [6, 27]. The overall treatment concept remained the same as in the preceding study HD-82 including involved-field irradiation with identical doses. Procarbazine was eliminated from OPPA, resulting in OPA, and replaced by methotrexate in COPP, resulting in COMP.

Results: Unfortunately, the results were disappointing, and we had to stop the study after 22 months. The proportion of early progression and relapses was unacceptably high. Especially in TG 2 and 3 the pEFS rates showed a rapid decline to about 50%. In the total group of all patients the long-term event-free survival was 70%. It has to be emphasized that the overall survival rate has not dropped owing to an effective salvage therapy (98% at 10-years). The evaluation of late effects in all 3 TG showed that those boys who remained in remission tested normal for endocrinic parameters of testicular function. Thus, the critical role of procarbazine for the testicular damage was clearly confirmed.

Study HD-90

In the most recent study HD-90 a second attempt was made to reduce the risk of testicular damage [28, 32]. We decided to exclude the girls from this particular trial as they have no disadvantage from the OPPA/COPP chemotherapy with procarbazine. The girls thus received the same chemotherapy as in study HD-82, whilst the trial objective was a further reduction of the radiation dose to 25, 25, and 20 Gy, respectively, in the 3 TG (Figure 5).

For the boys, etoposide was substituted for procarbazine in the initial two OPPA cycles, arriving at OEPA. All other details of the treatment plan, including radiotherapy and COPP cycles in TG 2 and 3, are identical to the schedule for the girls (Figure 5). The girls may thus serve as a control group to the boys for the evaluation of the changed chemotherapy.

In each of the OEPA cycles, etoposide is given at a dose of 125 mg/m² on 4 consecutive days, which adds up to a cumulative total dose of 1,000 mg/m² in the two cycles (Table 3).

Results: After 5 years, while final results cannot be given yet, a tendency can nevertheless be described. The values for pSV (Figure 1) and pEFS at nearly 5-years for the total group of 574 patients (girls and boys with all stages) are 99% and 90%, respectively, for the 257 girls 100% and 93%, respectively, and for the 317 boys 98% and 88%, respectively. No secondary leukemias have been observed until now.

Figure 6 shows pEFS by age groups. The curve representing the 15–18-year old adolescents shows no difference compared to the other two age groups. Thus, age up to 18 years does not appear to be of any prognostic significance with our therapy.

The curves representing the pEFS of boys and girls with localized stages, i.e., TG 1, are nearly super-

Table 3. Application and dosage of cytotoxic drugs in one OEPA-cycle.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>1, 15</td>
<td>40 mg/m² as 30 min. infusion i.v.</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1, 8, 15</td>
<td>1.5 mg/m² as i.v. injection (max. single dose 2.0 mg)</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>3 to 6</td>
<td>125 mg/m²/day as 60 min. infusion i.v.</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 to 15</td>
<td>60 mg/m²/day p.o. in 3 doses</td>
</tr>
</tbody>
</table>

Figure 5. Therapy schemes of study HD-90 for girls (a) and boys (b).
imposable at a high level (Figure 7a). Those subgroups represent nearly half of all patients. Therapy had consisted of only 2 cycles of OPPA or OEPA plus involved-field irradiation at a standard dose of 25 Gy. A local boost up to 30–35 Gy was given in 18% of patients. We tested more than 20 male patients above 15 years from this group endocrinologically and found no indication of testicular dysfunction.

The EFS curves of the intermediate stages II B and III A (TG 2) and of stages III B and IV (TG 3) are shown in Figures 7b and 7c. In both groups there is a slight difference between OPPA/COPP and OEPA/COPP, but without statistical significance so far.

Final conclusions from study HD-90 can be drawn only when the results have become more mature. At present it seems to be very likely that the results of this study will confirm that the reduction of radiation doses to 20–25 Gy in combination with OPPA or OPPA/COPP is possible without any impairment of the outcome. Moreover, in early disease stages 2 OEPA cycles seem to be equivalent to 2 OPPA. We hope that the OEPA/COPP chemotherapy will eventually also be proven as a good treatment for intermediate and advanced stages. Even a slight drop in the event-free survival rate with OEPA/COPP in boys compared to OPPA/COPP would still maintain a balance between cure rates and risk of late effects that is superior to most other published treatment concepts.

References


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