Treatment of childhood Hodgkin's disease without radiotherapy

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Treatment of childhood Hodgkin’s disease without radiotherapy

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Summary

Background: To minimize the side effects of treatment in children with Hodgkin’s disease (HD), chemotherapy was given without radiotherapy.

Patients and methods: From 1975 to 1984, 21 patients with HD having lymph nodes < 4 cm were treated with six MOPP courses. From 1984 to 1987, all children presenting with HD (n = 17) were given six ABVD courses. From 1987 to 1993 all children (n = 21) were treated with six alternating ABVD and MOPP courses.

Results: MOPP-treated children showed an event-free survival (EFS) of 91%, overall survival, 100%; ABVD-treated children had an EFS of 70%, overall survival, 94%; ABVD-MOPP-treated children had an EFS of 91% and an overall survival of 91%. Two cases developed a second malignancy. Toxicity was low.

Conclusions: In children, ABVD-MOPP treatment gives a good survival, and toxicity is low. Radiotherapy is not needed to treat HD in children.

Key words: chemotherapy, children, Hodgkin’s disease, late effects, secondary tumors

Introduction

Until 1975, we treated children suffering from stage I and II Hodgkin’s disease (HD) with extended-field irradiation (EF, 40 Gy). Patients with stage III and stage IV HD received MOPP chemotherapy in combination with extended-field irradiation. This treatment was similar to the schemes used in adults. The frequent occurrence of severe sequelae, including growth arrest of soft tissue and bone, hypothyroidism, gonadal dysfunction, and secondary malignancies, urged us to find other treatment regimens [1–4]. In Ugandan children, Ziegler et al. reported in 1972 a survival rate of 65% for clinical stage (CS) I and II patients after MOPP chemotherapy without radiotherapy [5]. From 1975 onward, we treated children with chemotherapy only. Up to 1984, radiotherapy was left out for all patients who presented with nonbulky disease, i.e., lymph nodes < 4 cm [6]. Since 1984, all children presenting with Hodgkin’s disease have been treated with chemotherapy only. At that time we also changed our chemotherapy from MOPP to ABVD, which was reported to be less toxic owing to the lower dosages of alkylating agents [7]. After treating 17 patients, relapses were seen in 5 children [8]. We considered this relapse rate too high. As combining ABVD and MOPP is in line with the Goldie hypothesis (i.e., the highest probability of cure can be achieved using non-cross-resistant drugs from onset), and because male gonadal function is reported to be reversible after three MOPP courses, we switched to the combination of ABVD and MOPP in all HD cases, irrespective of the stage or the size of the involved lymph nodes [9]. In this report, we give the data on all our patients treated without radiotherapy.

Patients and methods

From 1975 to 1993, all previously untreated children presenting with HD were considered for this study. Pretreatment evaluation consisted of a detailed patient history, physical examination, histologic examination of an involved lymph node, complete blood count, liver function tests, serum uric acid, chest X-ray, abdominal ultrasound, bone marrow aspiration, and trephine biopsy. In none of the children was a laparotomy with subsequent splenectomy performed. Staging was done according to the Ann Arbor recommendations. From 1975 to 1984, all patients (16 boys and 5 girls, ages 5 to 14 years, median 11 years) with nonbulky disease (lymph node diameter < 4 cm) were treated with six MOPP courses (this group is hereafter designated as the MOPP group). Patients with bulky disease did receive additional radiotherapy; these cases are not reported in this paper. From 1984 to 1987, we treated 17 children (12 boys and 5 girls, ages 3 to 15 years, median 11 years) with six ABVD courses (the ABVD group). From 1987 to 1993, 21 patients were treated with six courses of alternating ABVD and MOPP (sequence: ABVD-MOPP-ABVD-MOPP-ABVD-MOPP; the ABVD-MOPP group). Patient data on CS at diagnosis and histology are given in Table 1. In an effort to decrease the risk of lung toxicity, bleomycin was given in the ABVD-MOPP group of patients as six-hour infusion instead of by intravenous bolus injection.

Pulmonary carbon monoxide-diffusion (COD) was measured prior to every ABVD administration and at completion of therapy. Echocardiography was done prior to and after therapy. For statistical analysis of survival data, the Cox-Mantel test was used. For comparisons of pre- and post-treatment data, the Wilcoxon test was applied. For comparisons between the groups, a chi-square test using the Yates correction was used.

Results

In the MOPP group, 2 relapses occurred: An 8-year-old boy with CS III 18 months after diagnosis, who was rescued with 8 MOPP courses, and an 11-year-old girl
with CS III 11 months after diagnosis, who was rescued with ABVD courses. Event-free survival (EFS) in the MOPP group was 91% (SE 22.1); overall survival was 100%; follow-up period ranged from 120 to 264 months, median 153 months. In the ABVD treated group, 5 patients experienced a relapse: an 11-year-old girl with CS I, a 9-year-old girl with CS IV, an 11-year-old boy with CS I, a 14-year-old boy with CS IV, and a 13-year-old girl with CS III. Four were rescued with MOPP courses, in two cases combined with radiotherapy. The 13-year-old girl died from a secondary myelodysplastic syndrome (MDS) after 8 MOPP courses and total lymph node irradiation. EFS in the ABVD group was 79% (SE 14.7); overall survival was 94%; follow-up period ranged from 95 to 134 months, median 120 months. In the ABVD-MOPP group, 2 male patients (ages 15 and 16 years, with CS II and I disease, respectively) relapsed at 7 and 10 months. The first died despite MOPP courses combined with radiotherapy (40 Gy) from resistant disease. The second patient was treated with radiotherapy (40 Gy) only; this patient died from a later relapse, for which he was treated with dexamethasone, cisplatin, and cytarabine followed by an autologous bone marrow transplantation. EFS in the ABVD-MOPP group was 91% (SE 7.7); overall survival was 91%; follow-up period ranged from 31 to 94 months, median 76 months. There was no significant difference in EFS between the three treatment groups ($P = 0.14$).

### Late effects

In 2 children second malignancies were observed. In a patient from the MOPP group, a non-Hodgkin’s lymphoma occurred 10 years after initial treatment; he was treated with CHOP courses. He is (one year after these courses) alive and well. In the ABVD group a girl who relapsed and subsequently was treated with MOPP and total-node irradiation developed a myelodysplastic syndrome that transformed into AML; she died from complications during treatment.

Echocardiography did not reveal a decrease in left ventricular function in both ABVD- and ABVD-MOPP-treated patients. Although no clinical signs indicated decrease in pulmonary function in the ABVD-treated patient group, in 8 out of 17 patients a decreased CO diffusion was noted and 3 showed complete recovery. A decrease was seen in 5 out of 21 ABVD-MOPP-treated children (receiving six-hour bleomycin infusions). This difference was statistically not significant. In the MOPP group, virtually all male patients had severe gonadal damage (azoospermia and elevated FSH levels [10]). In the ABVD group, an increase for both LH and FSH was seen in 2 out of the 10 patients tested. In the ABVD-MOPP group, 10 of the 15 patients who reached adolescence were tested. Three patients had abnormal values; in one of these both FSH and LH were abnormal.

### Discussion

Since the introduction of MOPP chemotherapy in addition to extended-field irradiation, combined therapy has become a standard mode of treatment for HD in most centers [11, 12]. The first report on children treated without radiotherapy was from Ziegler et al. [5]. In 1978, Olweny et al. reported survival rates of 75% and 60% for low- and high-stage patients, respectively [13]. In 1988, Eckert et al. gave DFS rates of 92% for all stages using chemotherapy only [14]. In 1989, a randomized study showed equal results using chemotherapy with or without radiotherapy [15]. Recently, Lobo-Sanahuja et al. gave results on 86 children treated with chemotherapy with DFS rates of 90 and 60% for CS I–III A and III B–IV, respectively [16]. The reported decrease in DFS in patients with more advanced stages is not seen in our patients. But in our series only a few CS IV patients are included. This is, however, also the case in many other
reports. From a retrospective analysis on several reports, Bader et al. concluded that only CS IVB patients benefit from combined therapy [17]. The data from our patients are in line with the mentioned reports. The patients treated with only ABVD have, in our opinion, a lower disease-free survival rate. We cannot prove this statement, as we felt it unethical to continue the study until statistical significance would have been reached. It is striking that 4 out of 5 relapsing patients in our ABVD group could be rescued with further therapy, which is in contrast with 2 relapsed patients in our ABVD-MOPP group.

Considering long-term effects, it is known that ABVD courses combined with radiotherapy cause parenchymal lung damage. Gonadal toxicity is lower using ABVD instead of MOPP [18, 19]. The occurrence of secondary malignancies for MOPP or ABVD in combination with radiotherapy is probably similar [20]. However, no data on ABVD-MOPP-treated patients who were not irradiated are currently available in literature. Our patients show limited toxicity in combination with a good DFS. The limited number of patients showing hypergonadotropism is encouraging, but it must be emphasized that reproductive capacity can ultimately only be ascertained by (inducing) a pregnancy. Although we offer boys semen analysis, many young patients are understandably reluctant to do this kind of testing.

We conclude that ABVD-MOPP treatment without radiotherapy gives a high cure rate in all patients with HD. The treatment is safe, and data on late effects are favorable. However more patients are needed to draw definite conclusions.

References


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