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Gonadal Toxicity after Combination Chemotherapy for Hodgkin's Disease. Comparative Results of MOPP vs ABVD

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Abstract—*The comparative gonadal toxicity following two equally effective and non-cross-resistant regimens (MOPP and ABVD) was prospectively evaluated in 53 males with Hodgkin's disease. The median age was 29 yr (range 16-45). MOPP produced azoospermia in 28/29 patients (97%) while ABVD induced oligo-azoospermia in 13/24 patients (54%). Follicle-stimulating hormone levels were consistently and significantly increased after MOPP while their median value remained within normal range after ABVD. Sperm count was repeated in 34 patients. Recovery of spermatogenesis occurred in 3/21 cases treated with MOPP and in all 13 cases given ABVD. Present findings confirm that the two alkylating agents, mechlorethamine and procarbazine, included in the MOPP regimen cause sterility in most patients while the drugs included in ABVD are not associated with permanent gonadal dysfunction.*

INTRODUCTION

THANKS to modern approaches, about 70% of all patients with Hodgkin's disease can be offered a chance of cure [1, 2]. However, current research efforts should also attempt to decrease treatment-related complications. In particular, gonadal dysfunction represents an important iatrogenic toxicity which affects considerably the quality of life in young patients such as those with Hodgkin's disease.

Following the first observation about gonadal damage occurring in patients treated with cancer chemotherapy during the past few years, several reports have clearly indicated that the administration of drug regimens containing alkylating agents (e.g. mechlorethamine, cyclophosphamide, chlorambucil, busulfan, melphalan, procarbazine) and/or nitrosourea derivatives (e.g. carmustine, lomustine) is associated with frequent and permanent damage of spermatogenesis [3-9] and ovarian function [10-13]. During the past decade a number of prospective randomized trials have demonstrated that ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) is a polydrug regimen at least as effective as the classical MOPP regimen (mechlorethamine, vincristine, procarbazine and prednisone) in the treatment of intermediate and advanced stages of Hodgkin's disease [14, 15]. Moreover, our initial observations have suggested that ABVD is apparently devoid of some iatrogenic effects, namely sterility and leukemogenesis [14, 16], which are associated with the administration of MOPP chemotherapy.

In a randomized prospective study we have compared the effects of ABVD and MOPP treatment of Hodgkin's disease on gonadal function in male patients.

MATERIALS AND METHODS

Patient population

In a total of 53 out of 235 patients with biopsy-proven diagnosis of Hodgkin's disease and enrolled in a prospective randomized study testing MOPP plus radiotherapy vs ABVD plus radiotherapy [14, 15, 17], testicular function was evaluated at the end of the treatment program. This consisted of three cycles of either chemotherapy regimen administered before and after subtotal or total nodal irradiation. Prior to therapy patients were classified as having stage IIB, IIIA or IIIB. All study patients were in

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complete remission following combined treatment and in this group only subtotal nodal irradiation was delivered. All patients were under 45 yr of age at the time of gonadal analysis. In particular, in the MOPP group the median age was 29 yr (range 19-45) and in the ABVD group the corresponding age was 27 yr (range 16-41).

Seminal analysis

The median time from completion of treatment and semen analysis was 8 months (range 2-37) in the MOPP group and 6 months (range 1-80) in the ABVD group. A total of 34 cases (MOPP 21, ABVD 13) accepted to repeat the sperm count. The median time from first sperm analysis was 24 months (range 4-67 months) for MOPP-treated patients and 10 months (range 1-18 months) for ABVD-treated patients respectively.

Fresh semen was collected by masturbation after a 2- to 5-day period of sexual inactivity. The volume, concentration, motility and morphology of sperm were recorded in each case. Following the WHO criteria [18], we have classified azoospermia as the absence of spermatozoa in the ejaculate, and oligospermia as the reduction in sperm count to below 20 millions/ml.

Hormones

Hormone levels were determined in 42/53 males. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by specific double-antibody radioimmunoassay (Kit Biodata). Testosterone (TST) was measured by radioimmunoassay after extraction with PEG [19]. Laboratory normal ranges were as follows: FSH 5-15 mUI/ml, LH 5-15 mUI/ml and TST 3-9 ng/ml.

Statistical analysis

The statistical significance of differences in the incidence of oligo-azoospermia between the two treatments was calculated by the chi-square test with correction for continuity or by the Fisher exact test, depending on the number of observations. Since the hormonal data were skewed, the sample median rather than the sample mean was used as a measure of the average hormonal level for selected patient subgroups. Tests of significance comparing the values obtained in each subgroup were done using the Mann-Whitney U test.

RESULTS

Seminal analysis

Semen specimens from all 53 patients evaluated after cessation of therapy were analyzed and showed that 28/29 (97%) patients treated with MOPP chemotherapy were azoospermic. Recovery of spermatogenesis was observed in 3/21 patients after a median of 36 months (range 18-58) from first sperm analysis. In the 24 patients of ABVD group, azoospermia was observed in eight cases (33%) and oligospermia in five cases (21%). However, full recovery of spermatogenesis occurred within 18 months (median 10 months) from first evaluation in all 13 patients in whom the sperm count was repeated. The difference between the two groups is significant (Table 1).

Hormone evaluation

Estimations of FSH, LH and TST are shown in Fig. 1. In the MOPP group, FSH levels were consistently raised and their median value was outside the normal limits, with 19/25 estimations (76%) being abnormally high. In the ABVD group the median value of FSH levels remained within normal range, with only 4/17 estimations (23.5%) being above the upper limit of normal. All four patients had abnormal sperm counts (azoospermia in three cases and oligospermia in one case) at the time of hormone evaluation. The difference in FSH values between MOPP and ABVD groups reached statistical significance, with a P value of 0.001. The median LH and TST values were around the limit of normal in both treatment groups.

DISCUSSION

Numerous reports [3-9] have clearly confirmed that a few cycles of MOPP or MOPP-like combinations, such as MVPP (mechlorethamine,

Table 1. Comparative incidence of testicular damage following MOPP vs ABVD

	MOPP (29 cases)		ABVD (24 cases)		P
	No.	%	No.	%	
Azoospermia	28	97	8	33	<0.001
Oligospermia	0	—	5	21	
Recovered/reassessed	3/21	14	13/13	100	<0.0001
Median time in months (range)	36	(16-58)	10	(1-18)	

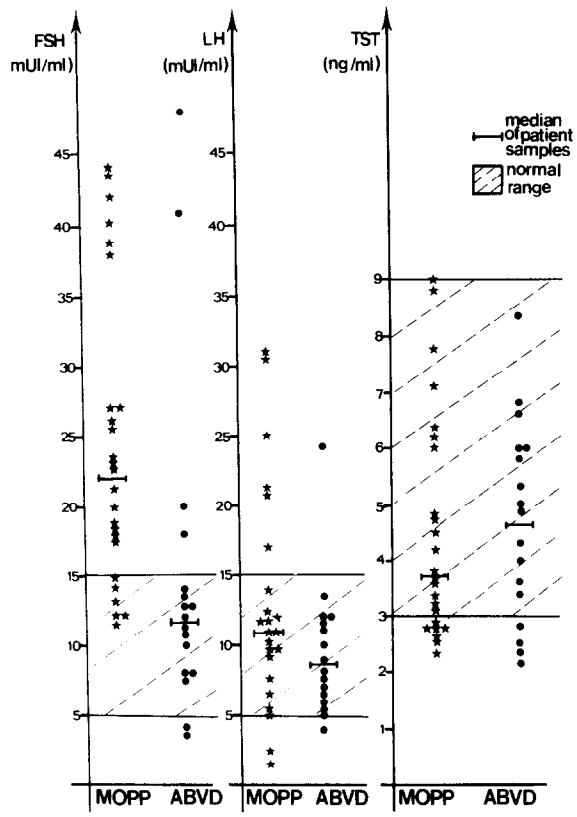

Fig. 1. Comparative values of FSH, LH and TST in patients treated with MOPP and ABVD chemotherapy. Testosterone, TST (ng/ml); *follicle-stimulating hormone, FSH* (mUI/ml); *luteinizing hormone, LH* (mUI/ml).

vinblastine, procarbazine and prednisone), induce azoospermia in 90–100% of patients and this finding is associated with germinal aplasia and increased FSH levels, with normal levels of LH and TST. In addition, only 10–20% of patients may eventually show recovery of spermatogenesis after long periods of time, even up to 10 yr. As recently reported by da Cunha *et al.* [20] the recovery rate is higher in patients treated with three or fewer chemotherapy cycles compared to patients receiving a higher number of cycles. The major groups of drugs responsible for the cytotoxic-induced gonadal damage are the alkylating agents mechlorethamine and procarbazine. In the adult male patients the effect is not age-related but is dependent upon the intensity of treatment, i.e. dose levels, number of courses and frequency of administration.

Our data with six cycles of MOPP chemotherapy confirmed the results previously reported by other investigators. In contrast, we observed that the administration of six cycles of ABVD chemotherapy produced only a limited and transient germ cell toxicity, and the difference in gonadal damage between the two treatment groups was significant. More important, the recovery of spermatogenesis in patients in whom the sperm count was repeated occurred in all instances in the ABVD group compared to only about 15% of patients treated with MOPP. Also, the median time to recovery favored ABVD, being less than one-third of that of MOPP. Other drugs, such as vinblastine [21], which is one of the ABVD components, have been incriminated to produce gonadal dysfunction. However, as observed in the present study, their effect on spermatogenesis was definitely less pronounced than that of alkylating agents since it was of lesser frequency and magnitude and, more important, completely reversible.

The reported results with MOPP vs ABVD in adult males are also supported by our findings in females with Hodgkin's disease. In a total of 61 women less than 45 yr of age who belonged to the same comparative trial and in whom the extent of radiation therapy was limited to para-aortic lymph nodes, we observed prolonged amenorrhea (no menses for more than 6 months) in 6/14 MOPP-treated women older than 30 yr while none of eight patients in this age group showed amenorrhea following ABVD. A full comparison on gonadal toxicity between the two drug combinations in women will require a more prolonged follow-up since ovarian failure secondary to cytotoxic chemotherapy is a progressive rather than an all-or-none phenomenon [11]. Our observed findings with ABVD are in keeping with the results reported in patients with soft tissue sarcoma [22], osteosarcoma [23], testicular cancer [24] and acute leukaemia [25, 26], where the administration of anticancer drugs other than alkylating agents induced only limited and transient gonadal dysfunction in both males and females.

In conclusion, to circumvent chemotherapy-induced sterility and therefore minimize the psychological and physical impact of chemical castration, the use of effective drug regimens not containing alkylating agents is highly recommended. An alternative for males undergoing MOPP or MOPP-like combinations is represented by sperm storage prior to chemotherapy. However, as recently published [27], about one-third of male patients with Hodgkin's disease have a low sperm count or sperm motility before starting cytotoxic treatment. This finding, which has also been confirmed by our experience in a series of 35 untreated males, reduces the percentage of patients for whom sperm banking may be indicated. The usefulness of other gonadal damage-preventing procedures such as the administration of analogues of gonadotropin-releasing hormone in males [28] or oral contraceptives in premenopausal women [29] remains to be fully confirmed.

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