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PREGNANCIES AFTER ENDOLYMPHATIC THERAPY OF RESIDUAL RETROPERITONEAL HODGKIN LYMPHOMA

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ABSTRACT

Three young women with Hodgkin lymphoma (stage III and IV) had residual retroperitoneal lymphoma after 6 cycles of standard chemotherapy. To preserve fertility, chemotherapy was subsequently continued as a single endolymphatic injection of 60 mg Bleomycin in oily suspension (Oil Bleo). Except for slight, transient fever in one patient, no side effects occurred. Follow-up plain X-rays with lipoidal stained lymph nodes showed a marked reduction in size of the retroperitoneal lymphomatous lymph nodes in all 3 patients.

Each woman became pregnant between 2 and 14 months after endolymphatic therapy and bore healthy infants. Two of the women remain free of disease. The third has had a recurrence in the neck and has been treated with second-line intravenous chemotherapy.

Endolymphatic therapy of retroperitoneal lymphoma may achieve a satisfactory result in selected patients while preserving fertility.

Disease-free survival has increased markedly since the introduction of potent cytostatic regimens for treatment of Hodgkin lymphoma. Yet these drugs potentially sterilize gonadal tissue and accordingly fertility should be considered in treatment decisions.

Non-cross resistant therapy with monthly alternating MOPP/ABVD (Mechlorethamine, Vincristine, Procarbazine, Prednisone/ Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) leads to complete tumor disappearance after a median number of five cycles; however, therapy extended to 12 or maximum 16 cycles is usually recommended (1). After this extended therapy, complete remission has been documented in 92 percent of women with stage IV disease. In comparison, therapy with MOPP alone leads to complete remission in 71 percent of patients.

Chemotherapy causes fertility disturbances. Only 3 of 45 men had normal testicular function after MOPP therapy (2). In a comparable study of 16 men, 4 had undisturbed testicular function (3). Amenorrhea occurs in about 50 percent of patients after MOPP therapy (2). This percentage has been confirmed in another study (4), in which women having regular menses after chemotherapy numbered 56 percent. The toxic side effects increased with the number of cycles (1). Chemotherapy has frequently been combined with radiotherapy in order to reduce the dosage of cytostatic drugs. However, ovarian function is dramatically impaired in women who received both chemotherapy and irradiation. As a result, reproductive potential is markedly reduced (4).

This report describes 3 young women with stage IIIb or IV Hodgkin disease who received modified (endolymphatic) therapy to minimize the risk of fertility disturbances.

CASE MATERIAL

TABLE 1
Staging and Results of Primary Chemotherapy

Patient	Age (years)	Hodgkin type	Hodgkin stage	Results (3months)
1	27	NS	IIIb	PR
2	26	NS	IV	PR
3	36	MC	IV	PR

NS: nodular sclerosis; MC: mixed cellularity; PR: partial remission

The histological type was based on the Kiel classification (5), which is essentially identical to the Lukes-Collins classification (6).

Stage IIIb or IV disease *(Table 1)* was diagnosed after conventional lymphography, chest X-ray, computed tomography, sonography, and biopsies with histological examination. Each patient underwent therapy consisting of 6 chemotherapy cycles (alternating MOPP/ABVD). The drugs in the MOPP regimen were: Mechlorethamine 6 mg/m2 and Vincristine 1.4 mg/m^2 were given i.v. on days 1 and 8. Procarbazine 100 mg/m^2 was given orally from days 1 through 14. Prednisone 40 mg/m^2 was given orally from days 1 through 14. The drugs in the ABVD regimen were as follows: Doxorubicin 25 mg/m^2; Bleomycin 10 mg/m^2; Vinblastine 6 mg/m^2; Dacarbazine 375 mg/m^2 given on days 1 and 15 of each cycle.

Three months after chemotherapy, follow-up studies documented residual subdiaphragmatic lymphoma without tumor at any other location. Three women (age range 26-36 years) refused both further standard chemotherapy or intraabdominal irradiation, even when prior midline oophoropexy was proposed.

After approval by the local ethics committee, newly designed (7-9) endolymphatic therapy with Bleomycin was performed. The procedure was as follows: The lymphatic vessels on both feet were cannulated according to the classic Kinmonth technique, and 5 ml of Lipiodal Ultra-Fluid (Byk Gulden Konstanz, Germany) was slowly injected by an automatic pump. After abdominal X-ray films confirmed the presence of residual lymphoma *(Fig. 1a)*, a total of 2 ml of Oil-Bleo (Nippon Kayaku, Tokyo, Japan) per foot containing a total of 60 mg Bleomycin was injected endolymphatically. Blood samples for Bleomycin were collected at set time intervals as shown in *Fig. 2*. The body temperature and leucocyte count were registered before and after therapy *(Table 2)*. The patients were asked whether they felt pain, nausea or other discomfort.

Abdominal X-rays were taken at regular intervals for monitoring, since the residual Lipiodal architecturally delineated the drug-filled lymphomatous nodes.

RESULTS

There was a marked reduction in size of residual retroperitoneal lymph nodes immediately after endolymphatic therapy *(Fig. 1b)*, remaining B-symptoms promptly disappeared and there were no notable adverse reactions *(Table 2)*.

As shown in *Fig. 2*, after a rapid initial rise in drug concentrations in the blood during injection, the Bleomycin concentration quickly declined and plateaued for many hours. The maximum amount of Bleomycin estimated in the serum at the end of injection varied from 0.48 to 3.8 mg *(Table 2)*, but was far below 15 mg, an amount which is routinely injected when given intravenously as a single injection.

All three women had undisturbed menses after therapy, and became pregnant within 2 to 14 months. The outcome of these pregnancies *(Table 3)* was satisfactory. In follow-up, 2 women remained disease-free (26 to 38 months), and the other has recurrence at the initial disease site in the left side of the neck.

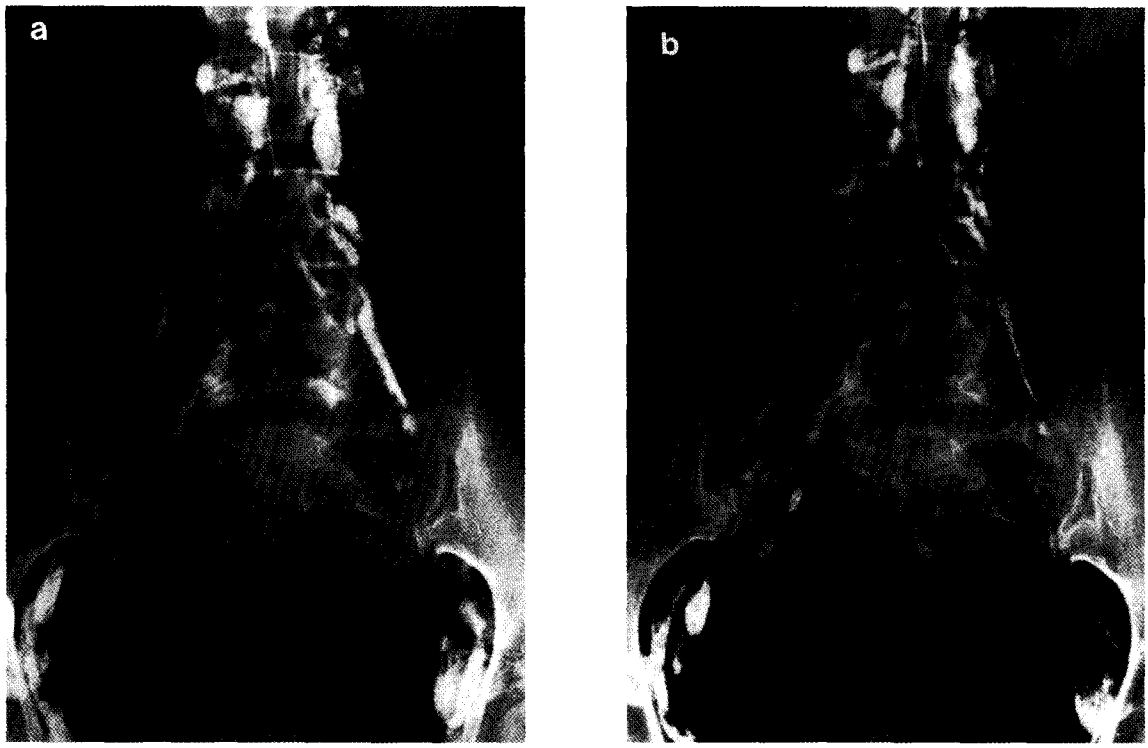

Fig. 1. Lymphography before (a) and after (b) endolymphatic therapy. Note marked reduction in size of retroperitoneal lymph nodes.

TABLE 2
Endolymphatic Therapy with Oily Bleomycin 3 Months after I.V.-Chemotherapy

Patient	1	2	3
total dose (mg)	60	60	60
max. concentration (ng/ml)	187	313	1519
max. amount in blood (mg)	0.48	0.78	3.8
percent of injected doses	0.80	1.3	6.3
leucocytes/mm^3	4300	4300	4400
leucocytes/mm^3 after 24 h	5200	2900	4000
fever day 1 (°C)	none	none	38°
adverse reactions	none	none	none

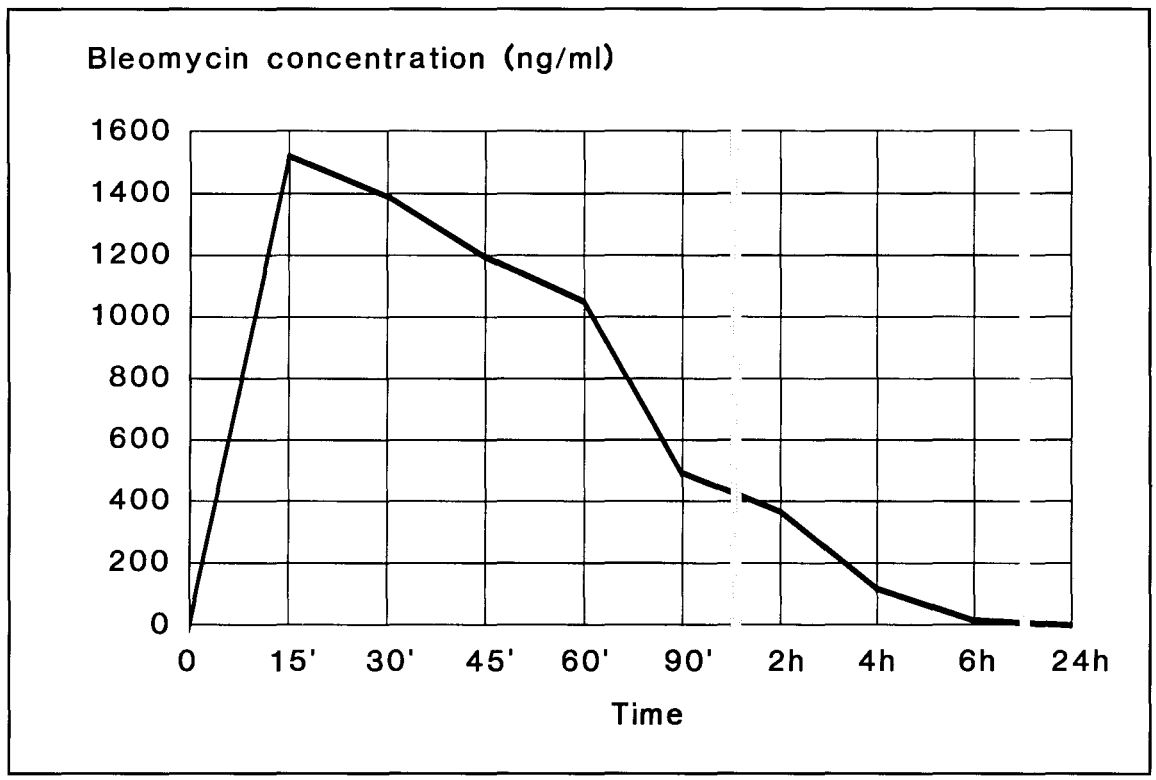

Fig. 2. Bleomycin levels in serum during (0-15 min) and after endolymphatic therapy.

DISCUSSION

Endolymphatic therapy was feasible in these patients after 6 cycles of standard chemotherapy because residual lymphoma was confined to the retroperitoneum. The conditions for endolymphatic therapy have been experimentally tested (7). Even after endolymphatic administration of high doses of Bleomycin (single dose of 60 mg per patient), drug spillover into the systemic venous system did not exceed tolerable serum concentrations and caused no major adverse reaction. Under experimental conditions, the Bleomycin is slowly released from its oily suspension and remains more than 4 weeks in therapeutic concentrations in the lymph nodes. Alterations in the histological structure of normal lymph nodes with Bleomycin are only slightly more pronounced than after standard diagnostic lymphography with Lipiodal (8).

After standard intravenous chemotherapy of Hodgkin disease, risks to pregnancy exist. Analysis of 28 pregnancies in 103 women after standard chemotherapy showed no spontaneous abortions, no birth defects or developmental abnormalities (4). However, pregnancies were least frequent in those women who had received both standard chemotherapy and intraabdominal irradiation. Only 20 percent of these patients had regular menses, and only half became pregnant after a median interval of 51 months following completion of standard treatment (4). In young women, it may be desirable, therefore, to avoid intraabdominal irradiation and consider endolymphatic (local) therapy instead. Even if the lymphoma recurs at a remote site (as occurred in one patient), established second-line chemotherapy options, including multidrug-polychemotherapy and irradiation, may still be used. In the

TABLE 3
Pregnancy Outcome

Patient	Pregnant after endolymphatic therapy within (months)	Duration of pregnancy (weeks)	Normal spontaneous delivery	Child weight (g)	Child length (cm)	Apgar score (at 1 min)	Health condition
1	2	40	yes	3240	50	9	normal
2	14	38	yes	2550	47	7	pneumonia within 10 months
3	9	37	yes	2650	48	8	normal

meantime, these women can enjoy disease-free and sequelae-free interval with their newborn infants.

In conclusion, selective treatment of residual retroperitoneal lymphoma using endolymphatic therapy allows good local control without adverse reaction and maximizes chance for normal pregnancy and delivery.

REFERENCES

1. Santoro, A, G Bonadonna, V Bonfante, et al: Alternating drug combinations in the treatment of advanced Hodgkin's disease. N. Engl. J. Med. 306 (1982), 770-775.
2. DeVita, VT: The consequences of the chemotherapy of Hodgkin's disease: The 10th David A. Karnofsky Memorial Lecture. Cancer 47 (1981), 1-13.
3. Sherins, RJ, DeVita VT: Effect of drug treatment for lymphoma on male reproductive capacity. Ann. Int. Med. 79 (1973), 216-220.
4. Horning, SJ, RT Hoppe, HS Kaplan, et al: Female reproductive potential after treatment for Hodgkin's disease. N. Engl. J. Med. 304 (1981), 1377-1382.
5. Lennert, K, RD Collins, RJ Lukes: Concordance of the Kiel and Lukes-Collins classifications of non-Hodgkin's lymphomas. Histopath. 7 (1983), 549-559.
6. Lukes, RJ, JJ Butler: The pathology and nomenclature of Hodgkin's disease. Cancer Res. 26 (1966), 1063-1981.
7. Hirnle, P: Endolymphatic application of Bleomycin oil suspension in dog model. Lymphology 18, (1985), 56-63.
8. Hirnle, P, N Geppert: Histologic changes in dog lymph nodes after endolymphatic application of bleomycin oil suspension. Lymphology 22 (1989), 100-102.
9. Hirnle, P, E Ziolko: Endolymphatic therapy of resistant bulky retroperitoneal Hodgkin lymphomas using bleomycin oil suspension. In: *Progress in Lymphology,* Cluzan, RV, AP Pecking, FM Lokiec (Eds.), Excerpta Medica (1992), 393-394.

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