USE OF CYCLOPHOSPHAMIDE (ENDOXAN) IN THE TREATMENT OF RETICULOSES

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The value of the nitrogen mustards in the treatment of Hodgkin's disease and related disorders has been known for many years. The limiting factor in their use has been their toxic action upon the bone-marrow and other tissues. Of the nitrogen mustards, cyclophosphamide (Endoxan) a cyclic nitrogen mustard phosphamide ester appears to be the least toxic.

This drug was first synthesized in 1958 by Arnold and Bourseaux. It is inactive when administered and is activated only on reaching the site where its therapeutic effect is required. For this conversion the enzyme phosphatases and phosphoramidases are required. Since malignant cells are rich in such enzymes it would appear that the drug is split to an active form within the tumour cells thereby inhibiting their activity. Reported below are the results of treatment of Hodgkin's disease and the related reticuloses using cyclophosphamide.

MATERIAL AND METHOD

30 patients of reticuloses were treated between 1960-1967. Of these, 11 suffered from reticulum cell sarcoma, 8 from Hodgkin's disease, 7 from lymphosarcoma and 4 from multiple myeloma. All these patients had wide-spread disease and were considered unsuitable for surgery or radiotherapy. 12 had an initial course of radiotherapy for localized disease but were subsequently referred for cytotoxic treatment because of recurrence. All the 30 patients had histological confirmation of the diagnosis.

Treatment commenced with an initial intravenous dose of 1 gm. after which each was observed for 2 weeks. Subsequently 400 mgm. weekly were administered. In the follow-up treatment as outpatients some received oral therapy of 50 mgm. to 100 mgm. daily. The drug was temporarily withdrawn when the total white —cell count fell below 3000 c.mm. or other toxic effects like alopecia or cystitis occurred. Regular blood examinations were made.

The effects of treatment were assessed by objective criteria and the patients' general well-being. These included control of fever, diminution in tumour size, gain in weight, correction of anaemia and return to gainful employment. Results following treatment were categorised thus:

0 — Clinical deterioration.
Treatment abandoned.

1 — Brief but significant remission.
Death within six months.

2 — Return to gainful employment or household duties
Survival more than six months with improvement of the disease.

RESULTS

HODGKIN'S DISEASE

This group gave the best results. Out of 8 patients, 5 responded well, 2 of whom having received continuous treatment up to 2½ years (see table) are now free from the disease. An initial but non-sustained remission was recorded in 3 others.

Three deaths occurred, 2 from spinal cord compression and one from fulminating chest infection (cytomegalic inclusion bodies demonstrated in lung sections after autopsy).

RETICULUM CELL SARCOMA

This group of 11 patients showed a poor response to treatment and none of them survived for more than 6 months although 4 patients showed initial response. 2 patients had gross infiltrative lesions of the stomach and presented as upper gastrointestinal haemorrhages.

USE OF CYCLOPHOSPHAMIDE (ENDOXAN) IN THE TREATMENT OF RETICULOSES: RESULTS

Case No.	Diagnosis	Previous Treatment	Dosage: Cyclophosphamide i/v (mgm)	Result
1	Hodgkin's Disease	—	15800	2
2	,,	DXT	26000	2
3	,,	—	1000	0
4	,,	—	5200 Oral	2
5	,,	—	1000	0
6	,,	—	800	0
7	,,	—	11000	2
8	,,	—	8000 Oral	2
9	Reticulum cell sarcoma	—	1000	0
10	,,	—	2000	1
11	,,	—	5000	0
12	,,	DXT	1000	0
13	,,	DXT	3000	1
14	,,	—	400	0
15	,,	—	1500	0
16	,,	—	3400	1
17	,,	DXT steroid	2000	0
18	,,	DXT	3000	1
19	,,	—	1000	0
20	Lymphosarcoma	—	3800	1
21	,,	—	11600	1
22	,,	DXT	1800	0
23	,,	Chlorambucil —	1400	0
24	,,	—	2000	0
25	,,	—	3000	0
26	,,	—	2000	0
27	Multiple myeloma	DXT	26000	1
28	,,	—	2000	0
29	,,	Urethane	3000	0
30	,,	DXT	27000	1

LYMPHOSARCOMA

There were 7 patients none of whom survived more than 6 months. 2 patients improved initially but rapidly deteriorated and became resistent to the drug.

MULTIPLE MYELOMA

There were 4 patients, 2 of whom showed some subjective but none any objective improvement.

DISCUSSION

Cyclophosphamide has proved satisfactory in clinical use and has the advantage of being least toxic of the alkylating agents.

Hodgkin's disease in particular can be treated fairly successfully with this agent. Matthias et al (1960) reported objective improvement in 11 out of 17 patients receiving cyclophosphamide. This is supported in the present series where 5 out of 8 patients showed objective signs of improvement (62%). Again, in 1963 Solomon et al reported significant benefit in 6 out of 19 patients with 7 others showing some beneficial effect from treatment.

As for lymphosarcoma and myelomatosis, evaluation cannot be undertaken here seriously as the number of patients was too small and most of the patients were in terminal stages. It would appear that cyclophosphamide, if at all, has only a limited role. It could be considered as an alternative when such patients are either hypersensitive or have failed to respond or became refractory to other agents.

Solomon et al in 1963 treated 8 patients suffering from lymphosarcoma with only 4 achieving some benefit.

Experiences with reticulum cell sarcoma elsewhere is even more limited. Anders in 1961 treated 4 such patients, all of whom died within 6 months with only two showing limited improvement. Solomon in 1963 treated 9 patients with reticulum cell sarcoma with 4 deriving some benefit. Likewise, only 4 out of 11 patients in this series experienced some alleviation of symptoms.

Cyclophosphamide can be recommended for treatment of Hodgkin's disease but its role in the other related reticuloses is uncertain.

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