VALUE OF CHEMOTHERAPY IN OVARIAN MALIGNANCIES

by

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Advanced ovarian malignancy is a grave condition which has posed a challenging problem for gynaecologists all over the world. It does not only kill but is the cause of much misery for the sufferer before death because of the associated ascites, oedema and pain. The traditional methods of treatment, namely, surgery and radiation therapy are of definite value in early ovarian malignancies—(Stages I & II), but have not given favourable results in advanced cases (Stages III & IV). The clinical staging referred to here is that adopted by the Mayo clinic and shown in Table I.

Table I.

Stage grouping for primary carcinoma of the ovary based on findings at clinical examination and surgical exploration.

Stage I—Growth limited to ovaries.

Stage IA—Growth limited to one ovary, no ascites.

Stage IB—Growth limited to both ovaries, no ascites.

Stage IC—Growth limited to one or both ovaries, ascites present with malignant cells in the fluid.

Stage II—Growth involving one or both ovaries with pelvic extension

Stage IIA—Extension and/or metastases to the uterus and/or tubes only.

Stage IIB—Extension to other pelvic tissues.

Stage III—Growth involving one or both ovaries with widespread intraperitoneal metastases in the abdomen (the omentum small intestine and its mesentery).

Stage IV—Growth involving one or both ovaries with distant metastases outside the peritoneal cavity.

Special category Unexplored cases which are thought to be ovarian carcinoma (explorative or therapeutic surgery not having been performed).

Once the metastases have extended to the upper abdomen, adjuvant radiotherapy did not give favourable results. Therefore, chemotherapy was tried at various centres. In 1957 Munnel, Jacox and Taylor reported remissions of advanced ovarian carcinoma with Thio-tepa. Later, in 1962, Miller and Brenner reported an improvement in the survival of patients with disseminated ovarian cancer by combining cobalt teletherapy with chlorambucil therapy. In 1963, Burns, Rutledge and Gallagher reported palliation with phenylalanine mustard.

Cyclophosphamide, Endoxan, was synthesized by Arnold and Bourseaux in 1957.

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Received for publication on 11-12-67.

It is a potent cytostatic agent related to the class of compounds known as nitrogen mustards. Neoplastic cells contain a large concentration of the enzyme phosphamidase. A molecule of the cytostatic agent cleaves to release the active form which is more toxic to cancer cells, than to normal cells. Endoxan Asta is reported to effect remissions in selected types of malignant neoplasms and it has proved to be a valuable protective therapy to prevent relapses in certain types of carcinomata and sarcomata, complementary to surgery and radiotherapy. The drug is usually well tolerated and the only significant side-reactions reported are nausea, vomiting, leukopenia, alopecia and a unique sterile haemorrhagic cystitis.

Relatively susceptible neoplasms are neoplasms affecting the lymphatic and reticuloendothelial systems comprising of Hodgkin's disease, lymphomas, lymphosarcoma, giant follicular lymphoma, reticulum cell sarcoma, leukemias and mycosis fungoides.

Relatively resistant neoplasms are those of the lung, gastrointestinal tract, breast and the genito-urinary systems.

This drug was reported to give fairly satisfactory palliative relief in advanced ovarian malignancies. So we decided to give it a trial. We had the chance to try it in four cases in the years 1965-66 in the following types of cases.

(a) Malignant granulosa cell tumour of the ovary with diffuse peritonial metastases and intestinal carcinomatosis—1.

(b) Teratocarcinoma with diffuse peritoneal metastases—1.

(c) Teratocarcinoma with pelvic peritoneal metastases—1.

(d) Krukenberg tumour with the primary lesion in the intestine and diffuse peritoneal metastases—1.

Laparotomy was done in all these cases and as much of the tumour and metastases removed as possible. In the first case, the case with malignant granulosa cell tumour, a panhysterectomy was done by a practitioner in a private nursing home. The patient came with a rapidly refilling haemoperitoneum within six months of the operation. Peritoneal tapping had to be done every third day to relieve respiratory distress. Laparotomy showed diffuse intestinal and peritoneal metastases. Omentectomy and excision of a big peritoneal metastatic mass was done and the pathological report came as malignant granulosa cell tumour of the ovary.

In the other three cases hysterectomy with bilateral salpingo-oophorectomy was done. But, due to involvement of several feet of intestinal loops which could not be resected, some tumour tissue was left behind. Omentectomy was done where the omentum was involved. Post-operatively we started all these patients on the cytostatic drug cyclophosphomide (Endoxan). We were fully aware that we could not expect a cure of the disease with the drug. The expected reward was only a relief from suffering and a possible prolongation of life. The patients' relatives were told about the limitations of the usefulness of the drug. Two of these cases, the one of malignant granulosa cell tumour and the other teratocarcinoma with only pelvic

metastases, were alive and fairly comfortable for 8 and 7 months respectively after the operation. The other two came with signs of intestinal recurrence within three months.

The case of granulosa cell tumour had developed ascites and a pelvic mass again by August 15th 1966. The ascites subsided with a second course of Endoxan. The case of teratocarcinoma has no palpable mass yet.

This line of therapy was selected because of the following reasons:-

1. Deep x-rays would have done more injury than help, since all these patients were in poor condition and the metastases were widespread involving the upper abdomen.

2. Injection of radioactive gold into the peritoneum is reported to slow the process of formation of ascites but has very little effect on gross metastases. The disadvantage is that it causes complications like intestinal obstruction, fistulae and peritonitis. Further, a chemotherapeutic agent secures a more even distribution of medication.

Method of administration and dose

We gave the drug by intravenous injection in dosage of 200 mg. every alternate day for 20 injections. Total maximum dose given was 8000 mg. Full haematological studies including platelet count were done before starting the therapy and weekly thereafter.

Toxic effects were few. Two cases developed mild nausea and vomiting which stopped on discontinuing the injections for a few days. In one case we had to discontinue therapy because the leucocyte count fell to 4000. But, after a week we were able to continue the treatment. There was no noticeable loss of hair in any of the patients.

Summary

In summary I would like to suggest that when faced with ovarian malignancy, resection of as much of the tumour as possible followed by a full course of Endoxan would help at least a few of the patients to lead a fairly comfortable life for about a year or more. Even that much is something gained and should be attempted.

Acknowledgements

(1) I wish to express my gratitude to the Medical Superintendent of the Miraj Medical Centre for permitting me to publish the hospital records.

(2) I am also grateful to the Dean, Goa Medical College, for allowing me to publish this paper.

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