BENEFIT VERSUS RISKS OF CHEMOTHERAPY IN GENITAL MALIGNANCY*

by

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The treatment of genital malignancy or for that matter any malignancy anywhere is far from satisfactory because of the obscure etiology and relatively late lesion during the initial diagnosis. Chemotherapy is one of the recent modalities of treatment either singly or in combination. A total massive dose consisting of multiple combination of drugs instead of fractional dosage for a prolonged period is considered a better alternative by quite a number of observers. The protagonists of such a therapy claim better action and consequent reduction of the undesirable side side effects specially on the erythropoiesis (Frei 1972; Serterelli and Creasey 1973).

The present study dates back from 1967 and envisages the use of different chemotherapeutic regime in different types of genital malignancy to assess the rationality of their use and the benefit accrued therefrom.

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Subjects Studied

Thirteen cases has been subjected to chemotherapy. This includes 1 case of sarcoma of the uterus, 4 cases of histologically proved trophoblastic malignancy (Choriocarcinoma), diagnosed by atleast two different pathologist, 1 case of suspected trophoblastic malignancy (Clinical choriocarcinoma) following molar pregnancy, 1 case of pseudomyxoma peritoneii and 6 cases of carcinoma recurring in the pelvis and/or vaginal vault following wertheim's operation with or without radiotherapy or only radiotherapy for carcinoma of the cervix uteri.

The following case records are worth considering to evaluate the current scope of chemotherapy in our hospital.

CASE REPORTS

Case 1

Sarcoma of the uterus: This case was already reported (Ghosh, A. K., 1973). Mrs. C.D. aged 73 years, para 11, widow for 6 years, having menopause for 25 years was admitted in the hospital on 27th December, 1967, complaining of a mobile lump in the lower abdomen and swelling of her right leg with anorexia, indigestion and sickness for quite sometime. Laparotomy revealed an inoperable case of suspected sarcoma of the uterus and a biopsy subsequently revealed round cell sarcoma of the

uterus (The size of the uterus conformed to 20 weeks pregnancy size). In the immediate post operative period the swelling of her right leg increased considerably and her anorexia with dyspeptic symptoms got worse. In the absence of anything better to do a trial of chemotherapy was considered. Inj. Cyclophosphamide was started intravenously daily (200 mg) from the 18th post-operative day and continued for two weeks. The treatment was controlled by frequent haematological examination with special reference to leucocyte and platelets. Within a week she had a sense of well being, the oedema became less marked, her appetite improved and she emphatically said that for the last many months she was never so well. At the end of two weeks there was complete regression of the abdominal mass and the oedema of the legs completely subsided. Pelvic examination revealed uterus 8-10 weeks size. Her haemoglobin varied from 65 to 70 per cent, W.B.C. ranged from 5 to 11 thousand per c.mm. and she had 600 mls of blood transfusion. After receiving 2,800 mg of cyclophosphamide she had rise of temperature of 101°F which could not be controlled by antibiotic and the chemotherapy had to be discontinued for a week. Oral therapy was started after the patient became afebrile with 50 mg tablet thrice a day for a week when nausea, vomiting and anorexia necessitated withdrawal of oral therapy to be followed by intravenous therapy. A total dose of 5850 mg was given in course of 5 weeks. The uterine enlargement retrogressed and the uterus became very small with negative curettings by Sharmann's biopsy curette. There was complete relief of subjective and objective symptoms. Alopecia was marked and with continued oral therapy anorexia and vomiting was marked. The patient discontinued the pills and died after 6 months due to sudden cardio-respiratory distress.

Choriocarcinoma

Case 2

Mrs. S.K.B. aged 56 years, Para 4 + 0, last child birth 14 years ago, had post menopausal irregular vaginal bleeding for six months. In the absence of any cervical lesion, a provisional diagnosis of Carcinoma of the body of the uterus was made because of the bulky uterus and at laparotomy a haemorrhagic blackish growth was seen in the uterus extending upto the serous coat of the uterus, one ovary was considerably enlarged and cystic. There was slight parametrial thickening on both sides. Total hysterectomy with bilateral salpingo-oophorectomy was done. The cuff of the vagina and a generous amount of parametrium was removed. Histological report from two different pathologists confirmed choriocarcinoma of the uterus. Urinary HCG was positive in 1 in 400 dilution. X-ray chest—negative. Haemoglobin 76 per cent and W.B.C. 7,200/c.mm. First course of Methotrexate 25 mg per day in divided dose was given orally for 5 days. The patient had anorexia, nausea, stomatitis and frontal alopecia. Haemoglobin was down to 65 per cent, W.B.C. 3400/c.mm. and platelets, 115000. The patient had 750 ml. of blood transfusion, Dexamethasone and Inj. vitamin B. Complex. Gradually the blood picture improved and a second course of therapy was given after 2 weeks with 20 mg Methotrexate daily for 5 days. Nausea and anorexia was very troublesome. Parenteral intramuscular iron and Vitamins were given. About 3 weeks after the initiation of the chemotherapy, the urinary HCG was positive in dilution 1 in 50 necessitating a third course of treatment, the dosage being the same as second course. Vomiting was controlled by sequil, 10 mg as and when necessary and Dexamethasone 5 mg tablet twice daily was given concurrently for a week. Urinary HCG became negative in a week's time. She had urinary infection once only during follow up. Patient is still under follow-up for little over 5 years and she is quite comfortable.

Case 3

Mrs. T.B. aged 24 years, para 3 + 0 was admitted with history of abortion at 12 weeks, however, the size of the uterus was more than 16 weeks and oxytocin induction failed to empty the uterus. In view of moderate bleeding continuing, laparotomy was done. While performing hysterotomy, the haemorrhagic necrosed growth in the uterus along with unilateral cystic ovary suggested the possibility of choriocarcinoma and a total hysterectomy was done. The post-hysterectomy specimen confirmed choriocarcinoma. Urinary HCG was positive in dilution 1 in 500, and X-ray showed a small circular pulmonary shadow in right lung along with diffuse mottling in both the lungs. First course of Methotrexate 25 mg daily orally for

5 days was given and repeated after 9 days. Blood transfusion 600 ml. Dexamethasone tablet, 5 mg thrice day for week and vitamin B. Complex was used as before. The patient had severe anorexia, nausea and vomiting along with the usual depressant effect on the bone marrow. A third course, 15 mg daily was given for 5 days 18 days after the second course since the urinary HCG was still positive in dilution 1 in 20. Urine was negative 6 weeks after surgery. X-ray chest negative. Patient is under follow-up for nearly 4 years.

Case 4

Mrs. R.N. 32 years, para 24 + 1. The patient presented as a case of incomplete abortion at 12 weeks of gestation with fever (101°F) and haemoptysis and the physician diagnosed her as a case of incomplete abortion with pulmonary tuberculosis. The patient had evacuation of the uterus along with antitubercular therapy. Due to recurrent bleeding she had three curettage at weekly interval, unfortunately the histological report of the curettings was not available. Haemoptysis continued. Suddenly the patient started with severe bleeding with pyrexia (103°F) and an emergency hysterectomy was performed when a necrosed perforating type of growth was seen which was subsequently confirmed as choriocarcinoma of the uterus. The urinary H.C.G. was positive in high dilution. A course of Methotrexate was given. The patient responded well and was discharged home after 8 weeks. After 6 weeks she came with haemoptysis with HCG titre in urine positive. Again the course of Methotrexate was repeated but the patient died in a week.

Case 5

Mrs. C.N. 30 years, para 3 + 0. had hydatidiform mole with toxaemia with the size of the uterus conforming to 28 weeks. Hysterotomy with sterilisation was done by ligation of the tubes. Urinary HCG was persistently positive 8 weeks after operation and the patient had haemoptysis. Abdominal total hysterectomy was done 8 months after hysterectomy as the patient could not be persuaded to come to the hospital. She had a course of post operative Methotrexate. Inj. Methotrexate 20 mg. daily for 5 days. Urine became negative after 2 more courses of therapy at the interval of 3 weeks. The patient is under follow up for about a year.

Case 6. Suspected clinical choriocarcinoma:

Mrs. G.D. 23 years, married 3 years, primigravida had spontaneous abortion followed by D and C for incomplete abortion when vesicular mole was found. After 5 weeks she required a repeat curettage of the uterus for profuse bleeding quite a moderate amount of vesicular mole was removed and the histological report suggested benign mole. Urinary HCG was persistently positive and on 23rd August, 1977 it was positive in dilution 1 in 25. Very slight vaginal bleeding and off and on Methotrexate 5 mg daily for 5 days has been given orally and at the end of a week urinary HCG has become negative. Patient is having some pain in the abdomen and some malaise. She is under follow-up.

Case 7. Pseudomyxoma-perotoneii:

Miss N.C. a young girl of 20 was operated for a ovarian cyst of 30 weeks of gestation size which turned out as pseudomucinous cyst adenoma of the ovary. Accidental rupture of the cyst during eventration of the mass was followed by pseudomyxoma peritoneii in 6 weeks time following ovariotomy. A fractional dose of cyclophosphamide 200 mg daily was given for 5 days and then the patient suddenly developed acute cardio-respiratory distress and died on the 6th day of chemotherapy. There was no appreciable change in the ascites.

RECURRENCE OF CARCINOMA IN THE PELVIS/AND/OR VAGINAL VAULT AFTER RADICAL ABDOMINAL HYSTERECTOMY WITH OR WITHOUT POST-OP. RADIOTHERAPY OR ONLY RADIOTHERAPY:

A total of 6 cases were included in this group. A total dose of cyclophosphamide 60 mg/kg of the body weight was given in single intravenous injection. It was combined with Mitomycin in some cases and Dexamethasone with Vitamin B 6, was also used concurrently in some cases.

Case 8

Mrs. K.M. 50 years multipara had recurrence of growth in the vaginal vault with extreme backache and radiating pain down the

legs following Wertheim's operation followed by Deep X-ray therapy 2 years ago for stage II carcinoma of the cervix. Suddenly she became comatosed and delirious with gross oliguria 600 ml of urine/24 hours and raised blood urea 230 mg. A total dose of cyclophosphamide (2 Gms) was given intravenously in single injection anl within 24 hours the urinary output was 1100 ml and the patient's condition improved considerably. She was put on oral regime, 50 mg tablet twice for the next 8 weeks. She was all right for the next two weeks excepting alopecia and progressive anorexia and died after 6 months.

Case 9

Mrs. R.B. multipara 40 years had Wertheim's operation for stage II carcinoma cervix. There was no metastasis in the regional glands. The patient came back with Vaginal bleeding with vault recurrence 3 months after surgery. A total dose of cyclophosphamide with Mitomycin 4 mg and dexamethasone 8 mg was given. The bleeding was completely controlled and the patient was discharged home. She is under follow-up for 9 months now.

Case 10

Mrs. M.Z. 40 years para 5 + 0 had Wertheim's operation for carcinoma of the cervix stage II, a year ago. She came with vaginal bleeding and pain in the abdomen. She had recurrence at the vault of the vagina and pulmonary metastasis in the way of multiple cannon ball shadow in both the lungs. Her body weight was 40 kg and she received a total dose with Mitomycin combination. First dose was given on 22-1-77 Inj. cyclophosphamide 2.4 Gm. Inj. Mitomycin-4 mg followed by Inj. Vitamin B6-200 mg and Inj. Decadren 8 mg. Haemoglobin value was down to 45 per cent from 62, W.B.C. count fell to 5,600 from 7,400 and platelets were 1,20,000 from 1,27,000/c.mm. Pulmonary shadows were reduced considerably and the bleeding completely subsided. The pain persisted. She had frequency of urination. Chemotherapy was repeated in 4 weeks time. Pulmonary shadow was further reduced but the patient had great deal of alopecia with anorexia and she was discharged on 9th of March, 1977. At the time of discharge there was no bleeding and the pain was considerably reduced.

Case 11

Mrs. B.M. aged 44 years, multipara had vault recurrence after Wertheim's operation followed by deep X-ray therapy for stage II carcinoma cervix a year ago in Jamshedpur. She was having pain in the back and irregular vaginal bleeding with anorexia and mild fever. Total dose of chemotherapy with combination of cyclophosphamide and Mitomycin along with blood transfusion could not give her any relief. The anorexia got worse, the pain and bleeding persisted and she is lost to follow up.

Case 12

Mrs. K.D. had pelvic recurrence and neurological involvement of the sciatic nerve following radiotherapy for carcinoma of the cervix stage III 6 months back. Her backache and radiating pain down the legs were excruciating in addition to vaginal bleeding on and off. She had a telecobalt therapy and felt better for 3 months when the symptoms recurred. Desperately a total dose of cyclophosphamide (60 mg/per kg) was given. There was initial response for 4 weeks followed by recurrence of distressing symptoms necessitating a second course of chemotherapy. The patient's condition deterioted. She became anaemic inspite of blood transfusion, the anorexia, nausea and alopecia were marked and soon she became disoriented with mild oedema of the face and feet. She was transferred to New York in semicomatosed condition by air where she had haemodialysis with blood transfusion, a course of repeat external radiation and nephrostomy (bilateral). About 3 months back she returned home in very good shape with good look, and provision of urinary drainage by disposable plastic bags tied round her thigh. She was advised to have Inj. Provera (long acting projestagens) weekly for next 6 months. She had all those injections but gradually her distressing symptoms recurred and she died about 9 months after returning from the United States.

Case 13

Mrs. G.M. 32 years multipara had Wertheim's operation for stage II carcinoma cervix. She had received telecobalt therapy 6 weeks after surgery. She was apparently well for 8 months and returned with limping gait, pain in the abdomen and back and inability to pass urine

without catheter. She had a local recurrence in the anterior vaginal wall just below the urethra. Urethro-cystoscopy did not reveal any abnormality. She was kept on continuous catheterisation with Foley catheter and simultaneously a combined chemotherapy, total dose was given along with Vitamin B 6 and Dexamethasone (1.5 Gm endoxan and 4 mg Mitomycin). She felt better, pain was considerably reduced. the appetite improved and the gait improved too. However, the urinary difficulty persisted and she could not do without catheter. Since urinary diversion was not possible, a second course of chemotherapy was given 3 weeks later and she was discharged back home with a plastic catheter for intermittent drainage. The patient died after six months.

Summary and Discussion

The remarkable response to chemotherapy by cyclophosphamide in the case of sarcoma of the uterus with complete regression of uterine growth of 20 week pregnancy size in an old woman of 73 with the relief of subjective and objective symptoms, is worth noting. The patient died after six months due to sudden cardio-respiratory arrest.

Complete regression of metastatic gestational choriocarcinoma following methotrexate treatment was first reported by Lei *et al* in 1956. Methotrexate was extremely beneficial in this small series of cases of choriocarcinoma.

The bizarre pattern of presenting symptoms in choriocarcinoma as post menopausal bleeding (case 2) and as septic abortion with haemoptysis (case 3) are worth remembering if one would not like to miss the diagnosis. Both the patients had remarkable recovery following combined surgery and chemotherapy. Post operative chemotherapy has given them a new lease of life which was beyond imagination a couple of decades from now. In case 6, a suspected case of clinical choriocarcinoma after removal of the molar pregnancy, a very small dose of Methotrexate, 5 mg daily orally for 1 week was good enough to make the urine free from HCG. However, the follow-up period is 3 years now. The recurrence of pulmonary metastasis following hysterectomy and post-operative Methotrexate with positive HCG which became negative 6 weeks back in a 32 year old parous woman (case 4) causing death suggests the unpredictable response in some cases, the cause of which is as yet obscure. We have no experience of reversing the depression of bone marrow by Folinic acid therapy. The use of cyclophosphamide in pseudomyxoma peritoneii was extremely discouraging.

The total combined dose of cyclophosphamide and Mitomycin in cases of recurrence of growth following Radical surgery/and or radiotherapy offered only an immediate short term benefit in the way of relieving pain, bleeding and urinary flow in one patient (case 8). The side effects like alopecia, anorexia, general malaise and anaemia were the distinct disadvantages. The poor results of chemotherapy following such recurrent signamous cell cercinoma after failed surgery and/or radiotherapy could be attributable to different factors. These are reduced vascularity and fibrosis due to poor blood supply consequent to previous surgery and/or radiotherapy causing deficient perfusion of the drug, reduced renal function and compensated bone marrow. A primary chemotherapeutic approach could probably be rewarding.

It is hoped that in near future a selective cancericidal drug without any effect on other tissues will brighten the scope of chemotherapy.

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