

Urea in the Management of Advanced Malignancies (Preliminary Report)

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Twenty cases of advanced (Stage III) cancer of the cervix were treated with intratumour injection of 40% urea solution and local application of 50% urea ointment. Sixty percent of these patients had beneficial effect and in 25% of the patients there was minimal response. Patients with multiple secondaries in liver had very good symptomatic relief with oral urea. Urea therapy is a simple, cheap, and safe method of treating advanced stages of cancer, where very little can be done by the accepted lines of treatment such as surgery or radiotherapy. This line of treatment can be practiced even in a consulting room or primary health center.

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Key words: urea, carcinoma of cervix, chemotherapy

INTRODUCTION

Carcinoma of the cervix is the commonest neoplasm seen in women in India. A majority of them come to the hospital in an advanced stage beyond the hope of any surgical cure. Most of our hospitals are not equipped with radiotherapy units. Palliative treatment of such patients with advanced cancers by some simple and safe method will be of great help to the patient in alleviating the agony of cancer.

Danopoulos and Danopaulou (3) reported on anticancer activity in urea, and they applied this property of urea as a chemotherapeutic agent in the treatment of skin malignancies and cancer of the liver. Pure urea is freely available anywhere in India and is not expensive. The present report is based on our preliminary observation in the treatment of advanced cancers with urea.

MATERIALS AND METHODS

For this study 25 patients with advanced cancers (Table I) with histologically proved diagnosis and beyond any hope of surgical cure, have been taken up. Of these, 20 had

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TABLE I. Type of Malignancy Treated

Epidermoid carcinoma of the cervix, Stage III	20
Osteosarcoma	2
Adenocarcinomatous secondaries in liver	2
Squamous cell carcinoma of the penis	1
Total cases	25

Stage III epidermoid carcinoma of the cervix, 2 had osteosarcoma, 1 with carcinoma of the penis, and 2 adenocarcinomatous secondaries in the liver.

All the 20 patients with cancer of the cervix were examined under general anesthesia, and those cases with extension of tumor into urinary bladder and rectum were excluded from the study. Biopsy of the growth was taken for histopathological examination, and the patients were treated with systemic antibiotics to control the secondary infection for 7 days. Once the biopsy report was available, urea treatment was instituted. Repeat biopsies of the cervix were taken at regular intervals. Two patients with biopsy-proved osteosarcoma refused any surgery and were unwilling to go to better centers for radiotherapy, and one patient with epidermoid carcinoma of the penis with fixed glands in both the inguinal regions was also included in this study. Two patients with multiple secondaries in the liver of adenocarcinomatous origin of unknown primary site were also included in the study. Both these patients were subjected to laparoscopic examination and percutaneous needle biopsy of the liver before institution of urea therapy.

Administration of the Drug

In all the patients with carcinoma of cervix, urea was given soon after the histological confirmation of the diagnosis was available. The patient was placed in lithotomy position. The vaginal walls were retracted with a Sim's speculum and anterior vaginal wall retractor. A 10 ml syringe was loaded with 40% sterile urea solution and with a long hypodermic needle, and 2 to 5 ml of solution was injected into the tumor mass in four quadrants around the cervical growth. The injections of urea solution were repeated every week for a period of 6 weeks. Simultaneously the vagina was plugged with urea ointment, and the patient was advised to continue this treatment for an indefinite period. (The urea ointment consists of 50% urea, 25% water, and 25% wool fat.) Biopsies from the growth were taken at regular intervals of 6 weeks. All these patients had regular blood urea estimations and total and differential white cell counts. Five patients were investigated by lymphography for the involvement of lymph nodes. Repeat x rays of the pelvis were taken 3 months after the institution of treatment to determine response (Fig. 1A and B). A similar technique was adopted for carcinoma of the penis.

For osteosarcoma patients and patients with secondaries in the liver, treatment with oral urea was adopted. Patients with secondaries in the liver underwent liver function tests and blood urea estimations before starting treatment and at regular intervals. Two grams of urea powder dissolved in glucose water every 6 hr was given by mouth, and the patients were advised to continue the treatment indefinitely.

RESULTS

Cancer of the cervix (Table II). All patients were kept in the wards for 2 to 3 months and later were requested to attend as outpatients. They were advised to continue the application of urea ointment.



Fig. 1. (A): Lymphography showing metastatic secondaries in the inguinal and external iliac lymph nodes.

(B): Repeat x ray taken 3 months after the institution of treatment showing marked reduction in the size of the lymph nodes due to reduction in the metastatic secondaries following treatment with urea.

TABLE II. Results of Treatment with Urea in 20 of Advanced Cancer of the Cervix

Outcome	Period of follow-up		Total	
	3-6 months	6-12 months		
50-75% reduction in size of growth	3	4	7	(35%)
Stage III converted to Stage I	3	—	3	(15%)
Minimal responses: 25-50% reduction in tumor size	4	3	7	(35%)
No benefit	3	—	3	(15%)
Total cases	13	7	20	(100%)

In 7 patients (35%) the growth regressed in size by 50% to 75%. The cervix, not visible before the institution of this treatment, could be made out clearly at the end of 6 weeks of treatment. Following the injection treatment the tumor sloughed off, resulting in small nodular areas in the region of the cervix and vagina. Induration in the parametrium had disappeared. Of these 7 patients 4 were feeling comfortable and gained in weight; discharge was minimal at the end of 6 months of treatment. All these patients were con-

tinuing the application of urea ointment. The remaining 3 patients, who had shown beneficial effects following the urea injections and ointment application, discontinued the treatment after 4 months. They returned with reappearance of the growth and foul-smelling discharge. Again, they were put on the injection treatment and local applications of ointment with a resultant reduction in the tumor.

In 3 patients (15%) there was a marked reduction in the size of the tumor with Stage III cancer of the cervix becoming Stage I; it became possible for 2 of these patients to be operated on for radical hysterectomy (Fig. 2A and B). Four other patients showed minimal response, that is, only 25 to 50% of tumor tissue disappeared in the first 2 months; there was no further appreciable response even after repeated injection of 40% urea solution. Two patients in this group were referred to a different center for radiotherapy, after

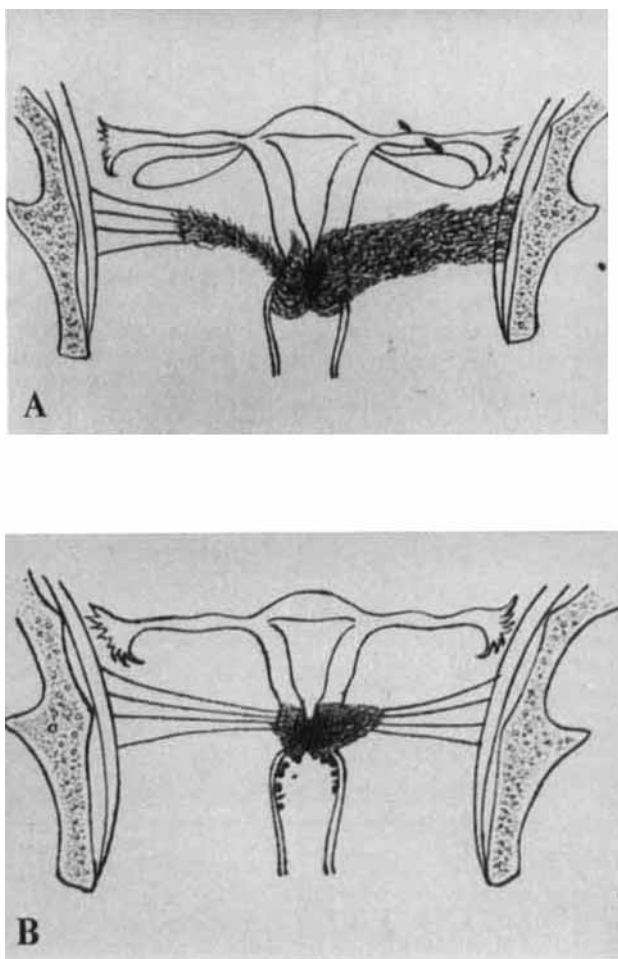


Fig. 2. (A): Diagrammatic representation of Stage III cancer of the cervix.

(B): Diagrammatic representation showing Stage III cancer of the cervix reverting to Stage I, making it possible that radical surgery be performed.

which they came to feel very much better and the tumor reduced in size. Three patients who had alternate day injections developed very severe bleeding following 40% urea solution injections, and they required repeated blood transfusions. Because of this bleeding following injections, only ointment application was continued, and further progression of the growth was controlled for the last 4 months. Later on, in the rest of the patients the injections were made at weekly intervals, and there was a 25 to 50% reduction in the size of the tumor. One patient died of pulmonary embolism 4 days after the injection of 40% urea solution. We cannot determine any definite relationship between the injection of urea solution and pulmonary embolism. In 2 patients in spite of repeated injections of 40% urea solution and urea ointment application the disease progressed rapidly.

Osteosarcoma. Oral urea treatment was adopted in 2 cases who refused surgery and for whom radiotherapy was not possible, as the patients were not prepared to go to a different center. The responses to oral urea therapy was poor and the tumor fungated through the skin with development of multiple secondaries in the lungs. Both the patients died within 3 months of the institution of this treatment.

Cancer of the penis. The primary tumor regressed in size markedly following urea injections and application of ointment. The lymph nodes reduced in size appreciably.

Multiple secondaries in liver. Both the patients showed very good clinical response following oral urea. In 1 case with adenocarcinomatous secondaries, the size of the liver reduced by 6 cm, itching due to obstructive jaundice disappeared, and serum bilirubin levels dropped from 37 mg % to 20 mg % in a period of 1 month. He felt very much better and his appetite improved. He was feeling much better by the end of 3 months after starting oral urea treatment. However, his serum bilirubin levels and other liver function tests remained stationary after an initial improvement. The second patient with multiple secondaries in the liver has been treated with oral urea for the last 1.5 months and is feeling better without much clinical progression of the disease. In both these patients, the primary tumor was not localized, and laparotomy was not performed as the patients were not fit for any major surgical procedures.

Histological changes (Cancer of the cervix). Prior to the institution of this line of treatment all the biopsy specimens showed the tumour cells infiltrated into the deeper parts of the cervix in the form of sheets with very little fibrous tissue in between. Sections taken from the nodules from the cervix 10 weeks after institution of this line of treatment showed atrophic changes of the tumor cells surrounded by heavy fibrosis.

Complications (Table III). All the patients complained of pyrexia of 100 to 101°F after every injection of 40% urea solution for 24 to 48 hr.

Four patients with cancer of the cervix and 1 patient with cancer of the penis complained of a severe burning sensation at the site of injection and it lasted for 15–30 min. In the beginning, when urea powder was applied after creating a raw area in the tumor, the patients complained of burning in the vagina and refused to use urea powder. Once the ointment was applied instead of powder they did not have any complaints. Three patients with cancer of the cervix had severe bleeding due to sloughing following 40% urea solution injections. In these 3 patients, repeated blood transfusions were required, and urea injection had to be abandoned.

One patient with osteosarcoma complained of symptoms suggesting gastric irritation following oral urea therapy. To avoid gastric irritation the patients were advised to take some antacid preparation along with the urea solution.

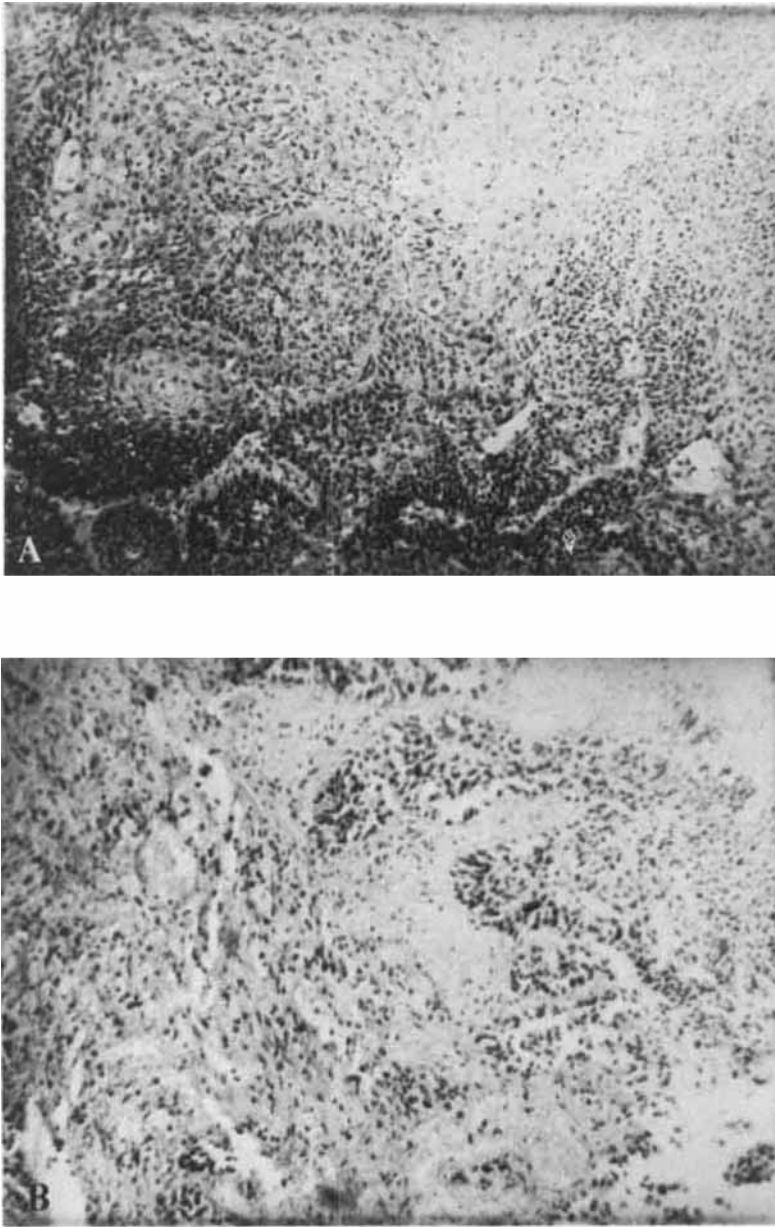


Fig. 3. (A): Microphotograph showing moderately differentiated epidermoid carcinoma with infiltration into the deeper parts of the cervix.

(B): Histopathology of the cervix of the same patient 2 months after urea treatment showing heavy fibrosis with atrophic changes of the tumor cells. Diffuse patterns of tumor cells are not noticed in this section.

TABLE III. Complications (Side Effects)

1. Fever (100–102°)	20
2. Pain at site of injection	5
3. Severe bleeding	3
4. Gastric irritation with oral urea	1

DISCUSSION

Various methods of treatment have been adopted in the management of cancer of the cervix, such as surgery, radiotherapy, and chemotherapy (5). Cancer of the cervix can be adequately controlled by surgery and irradiation in most instances if it remains localized and does not invade surrounding tissues or metastasize. However, successful treatment of widely disseminated cancers will depend on the discovery of agents that can be administered systemically. The drugs used at present are unfortunately by no means perfect anticancer agents (2).

In view of the fact that chemotherapy against cancer is not yet sufficiently fully established to compete with the main forms of treatment — surgery and irradiation — most of the clinical trials have been strictly confined to hopeless, advanced, or recurrent cases, where the main therapeutic measures have failed.

Many chemotherapeutic agents like methotrexate fluorouracil, hormones, hydroxy-urea, Abrin and Ricin (extract isolated from plants indigenous to Taiwan), etc., have been used in the treatment of cancer of the cervix with different types of response (1). They have been given by various means: Parenteral, intraarterial, and local perfusion, intratumorous injection, and local application. The results have been varied.

Instituting chemotherapy requires that a patient have a histologically proved malignant disease, positively established to be beyond any hope of surgical cure.

Danopoulos and Danopoulou (3) observed anticancer activity in urea, and they have treated the effects of this agent in liver cancer and skin malignancies. They achieved 73% benefit with the injection of urea solution alone, and when injection was combined with scraping off and treatment of the traumatized surface with urea powder, the benefit rate was 91%.

We adopted this technique in cases of Stage III carcinoma of the cervix, where treatment by surgery is not possible and radiotherapy is purely palliative and not universally available. Most of our patients come to the hospital in the late stages. To these unfortunate patients any form of therapy that gives even symptomatic relief is of great help. As urea is freely available and cheap we wanted to try this line of treatments, and we had a benefit rate of about 60%. In 3 patients, Stage III cancer of the cervix had changed over to Stage I and for two of them radical surgery became possible. All the patients who showed beneficial effects gained in weight, and foul-smelling discharge disappeared. Histologically there was a great amount of fibrous tissue deposition and necrosis with sequestration of malignant cells. At some places atrophic changes of malignant cells were noted, but disappearance of malignant cells as reported by Danopoulos and Danopoulou (3) was not observed. How the urea acts as an antimalignant cannot be explained, but we feel that

urea has some cytotoxic effects. It is also felt that urea produces irritation and fibrosis, leading to the conversion of cellular tumour into a scirrhous carcinoma.

Donopoulos and Donopoulou (3, 4), also reported that oral urea was useful in producing regression of liver cancer in 18 patients. Eight patients had primary carcinoma and 10 had tumor with liver secondaries. They found oral urea treatment to be more effective in primary carcinoma of the liver. We adopted oral urea treatment in two cases of adenocarcinomatous multiple secondaries in the liver. These patients showed marked reduction in the size of the liver, itching was less intense, appetite improved, and the patients gained an average of 4 lb, over a period of 2 months. These patients are alive at the end of 3.5 months and feeling very much better.

Oral urea, however, was not effective in 2 cases of osteosarcoma who refused any surgical intervention or radiotherapy. Both these patients developed multiple secondaries in the lungs with extension of the tumor to the skin, resulting in fungation under the treatment of the urea, and death.

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