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Combination Cisplatin and Dichloromethotrexate in Patients with Advanced or Recurrent Cervical Cancer: A Preliminary Report[1]

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The chemotherapy combination of cisplatin and dichloromethotrexate was administered to 14 patients with measurable cervical cancer. Six (46%) have had a complete response for 6+, 7, 11, 14, 15, and 21 months. Four (30%) have had a partial response for 1, 6, 10, and 11 months. Two patients (15%) have had stable disease for 6 and 11 months. Only one patient failed to respond to this combination. In six of these patients, the measurable mass was located in a previously radiated area. This combination was well tolerated with only three instances of severe toxicity. No irreversible renal dysfunction was seen in any patient.

The treatment of cervical cancer has, for the most part, been successful. This is due to its propensity to remain confined to the pelvis. However, in those patients where it has spread beyond the confines of the pelvis or it persists in spite of maximal radiological and surgical therapy, the therapeutic thrust must fall to chemotherapy. Numerous agents have been tested in this tumor system, but none have demonstrated significant activity [1–5].

Preliminary data from the University of Michigan suggest that the combination of cisplatin and dichloromethotrexate has exceptional activity against this neoplasm. This has been accomplished with a low toxicity rate seldom seen in combinations used against cervical cancer.

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METHODS AND MATERIALS

Patients included in this study were required to have (1) pathologically confirmed cervical cancer not amenable to any surgical or radiological therapy; (2) measurable disease; (3) no prior treatment with any chemotherapeutic agent; (4) normal function of the bone marrow, liver, and kidneys; and (5) signed informed consent. Fourteen patients met these criteria and were included in the study. Basic characteristics of this group are seen in Table 1. There was an even distribution of initial stage seen in this group (Table 2). The site of recurrent measurable disease was found in the pelvis, abdomen, or lungs (Table 3). Measurable disease was followed by pelvic exam, appropriate X rays, and/or CT scans. In the case of pelvic disease, six patients had previously received in excess of 5000 rad to the lesion under treatment.

Cis-Diamminedichloroplatinum II (cisplatin) (NSC-119875) was administered intravenously every 4 weeks at a dose of 60 mg/m^2 over 2 hr. Various antiemetics were given in conjunction with this infusion to aid in the control of nausea and vomiting. Following completion of this infusion, a 24-hr period of intravenous hydration ensued.

3′,5′-Dichloro-4-amino-4-deoxy-N^{10}-methylpteroyl-glutamatic acid (dichloromethotrexate) (NSC-29630), supplied by the National Cancer Institute (Bethesda, Md.), was given intravenously on a weekly dose-seeking schedule. It was started at a dose of 300 mg/m^2 and increased by 100 mg/m^2 each week until toxicity developed. In most cases, the final dose was 600 mg/m^2.

The objective response to this regimen was assigned according to the standard definitions: complete remission (CR)—disappearance of all clinical evidence of tumor on physical examination or X-ray evaluation for greater than 1 month; partial remission (PR)—50% or greater decrease by physical or radiological examination in the sum of the products of the perpendicular diameters of all measurable lesions for greater than 1 month; stabilization (STAB)—50% decrease in measurable disease for greater than 2 months; and progression (PROG)—any increase in measurable disease or the appearance of any new lesion.

TABLE 1
PATIENT CHARACTERISTICS

Histology	
Squamous	11
Adenosquamous	2
Age (average)	54 (35–78)
Course to response	3 (1–4)
Prior treatment	
Radiation	9
Radiation + surgery	3
None	1
Surgery only	0
Chemotherapy	0

TABLE 2
INITIAL STAGE OF DISEASE

IB	3
IIA	1
IIB	2
IIIB	2
IVA	4
Unknown	4

RESULTS

One patient died of disease after only one course of drug, leaving 13 evaluable patients. In the 13 evaluable patients CR was seen in 6 (46%), PR in 4 (30%), STAB in 2 (15%), and PROG in only one (8%). When the individual response groups are examined, the length of response for the CR group averaged 12.3+ months, while survival averaged 18.8+ months. In the PR group, these figures are 7 and 11.5+ months, respectively. Of the 10 responders, 7 are alive with disease, 2 have died of disease, and one died while in CR.

These results were obtained with minimal major toxicity. Since a dose-seeking schedule was used for the dichloromethotrexate, all patients developed some toxicity. In most cases this was a self-limited stomatitis. Once the drug's maintenance dose was established, no significant toxicity was seen in the majority of patients. Severe toxicity was seen in only four cases. Two women experienced neurotoxicity with ataxia developing. A complete workup of both suggested that the toxicity was secondary to platinum. Both showed nearly complete resolution of symptoms when platinum exposure was stopped. A third woman experienced one episode of pancytopenia (WBC < 1000, platelets $< 25{,}000$) which resolved when drug administration was suspended. She was restarted at a lower dose and experienced no additional toxicity. A fourth woman developed severe thrombocytopenia, a skin rash and cardiovascular collapse. She represents a drug-related death. No woman showed any severe renal damange resulting from the treatment regimen.

DISCUSSION

Two of the most active chemotherapeutic agents against cervical cancer are methotrexate [3] and cisplatin [6]. The combination of these two drugs has resulted in intolerably severe methotrexate toxicity which has been attributed to impaired renal clearance often resulting from cisplatin toxicity [7]. However,

TABLE 3
SITE OF MEASURABLE RECURRENT DISEASE

Pelvis	8
Abdomen	1
Lung	4

dichloromethotrexate, a dihalogenated analog of methotrexate, is an active antifolate and is excreted more by biliary than by urinary routes, therefore, allowing potential combination with cisplatin in full doses. It was this lack of a common excretory pathway that suggested the potential success of this two drug regimen against cervical cancer.

This preliminary work suggests that squamous cell carcinoma of the cervix is quite sensitive to the combination of cisplatin and dichloromethotrexate. In addition, this combination seems to be able to maintain this response and results in a significant increase in the length of survival. This level of response is even seen in those cases when the recurrent malignancy is located in an area previously treated with radiation thereapy. More importantly, this success is obtained with few untoward side effects. Most women have been able to maintain their normal activities; thus, both survival and quality of life are improved.

One of the disadvantages of this combination is the presence of nausea and vomiting and the prolonged hydration time associated with cisplatin. In view of the fact the average woman shows a maximal response after three to four cycles of drug, it would be of interest to see if a remission could be induced with this combination of drugs and maintained with only dichloromethotrexate. Such an approach would minimize the untoward effects of cisplatin. This was found to be a successful program in the two women who could not continue to receive cisplatin because of neurotoxicity.

At the present time work is underway to test this combination in a larger group of women in an effort to confirm these highly encouraging preliminary results.

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