Is the combination of mitomycin C, bleomycin and methotrexate effective as a neoadjuvant treatment for cervical cancer in women?

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Summary

Objective: To determine the effectiveness of the combination of mitomycin C, bleomycin and methotrexate as a neoadjuvant treatment in preparation for surgical treatment of cervical cancer. *Methods and Materials:* Twenty-seven patients with carcinoma of the uterine cervix (stages exophytic IB2 and IIB-IIIB) who had not previously undergone any treatment received mitomycin C, bleomycin and methotrexate in five sessions, once every four weeks. *Results:* The objective response rate was approximately 81%, including 16 complete responses and six partial responses. Significant toxic effects were not observed. Responsive patients underwent surgery and remained without evidence of disease for the next 20 years. Unresponsive patients did not fare well and passed away within five years after treatment. *Conclusion:* Our data suggest that this strategy may be effective for advanced cases, enabling patients to receive surgical treatment.

Key words: Bleomycin; Mitomycin; Methotrexate; Cervical cancer; Chemotherapy.

Introduction

Uterine cervix cancer (in its diverse histological types and clinical forms) is among the most frequently occurring female tumors in developing countries [1]. The average after-treatment life span of five years is inversely proportional to the clinicopathological stage of the tumor. Thus, patients with tumors in Stages IA and IB have a remaining life span of five years in 88% and 98.5% of cases, respectively, and the lymphatic nodules are compromised in 20% to 30% of the cases. In Stages IIA and IIIB, the percentage of patients with 5-year survival decreases to 65% and then drops further to 14% to 15% when tumors are in Stage IV. Lymphatic nodules are involved in 30% to 50% of cases in Stage II and in 60% or more of cases in Stages III and IV [2].

Surgery and radiotherapy are adequate and effective treatments for tumors in the early Stages (I and II). However, the remaining after-treatment life span is directly related to the volume of the tumor and, above all, to the extent to which the lymphatic nodules are compromised [3, 4]. In fact, good results have also been achieved for tumors in Stages I and II, especially for those of smaller size, when they were submitted to partial or total hysterectomy with or without radiotherapy [5]. The exception is the exophytic cervical tumor in Stage IB2; it is usually voluminous, making the surgical approach difficult [2].

Satisfactory results have not been obtained for tumors in Stages III and IV submitted to surgical therapy and/or radiotherapy. In this situation, the prescribed treatment includes adjuvant chemotherapy. This, however, is a palliative therapy chiefly applied to recurrent tumors not amenable to surgical or radiotherapeutic treatment or to metastatic tumors, or as surgical and/or radiotherapeutic post-treatment [6]. Despite advances in modern chemotherapy, results have not been satisfactory when using this technique [7]. Hence, uterine cervical carcinoma may be considered to have low sensitivity to chemotherapeutic agents [6]. Previous therapeutic failures might be partially attributed to the non-ideal conditions in which adjuvant chemotherapy has been employed. For example, in relapse cases, areas previously submitted to radical surgery hinder the diffusion of antiblastic agents at ideal pharmacological concentrations and cause a large percentage of cells to enter the resting phase due to vascular deficit and hypoxia [8, 9].

Antineoplastic chemotherapy can employ mitomycin C, whose mechanism includes cross-linking of several types of DNA, the promotion of DNA degradation and the inhibition of DNA synthesis [10]. Bleomycin is isolated from *Streptomyces verticillus*. Like all antitumoral antibiotics, it is a bacterial product that can inhibit the proliferation or function of cancer cells by preventing the incorporation of thymidine into DNA, thus inhibiting synthesis [11]. Bleomycin appears to exert a specific clinical effect on the epidermoid type of carcinoma. Methotrexate inhibits folic acid reduction during DNA synthesis in cell replication [12]. Chemotherapeutic agents act in different phases of the cell cycle; thus, the use of different combinations of drugs not only allows the expansion of the chemotherapeutic scheme but also makes it possible to reduce the doses of each agent. The desired effects can therefore be increased while toxicity is decreased [6].

There are few data regarding neoadjuvant chemotherapeutic treatments with the combination of mitomycin C, bleomycin and methotrexate and possibly followed by

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surgery in women with uterine cervical carcinoma. Thus, this study aimed to evaluate the effectiveness and adverse reactions of this treatment with a 20-year follow-up.

Methods and Materials

This was an open-label, prospective study with 27 volunteers selected from 60 women with uterine cervical neoplasia between May 1980 and May 1985. All of them had either exophytic tumors in Stage IB2 or tumors in Stages IIB-IIIB. These were the inclusion criteria: absence of distant metastasis and of previous treatment for another type of cancer as well as contraindication for chemotherapeutic agents (cardiovascular disease and anemia of unknown etiology). Furthermore, women over the age of 75 were not included. Before starting therapy, all women were informed of the protocol, and they signed an informed consent to participate. The study project was approved by the ethics committee of the institution. Participants were submitted to a neoadjuvant chemotherapeutic scheme. Ages ranged from 27 years to 68 years.

To measure the diameter of the cervix before and after treatment, we developed a device to measure the largest diameter of the uterine cervix. The device had two 15 cm-long aluminum stems with fixed articulations between them, and at the point where the two stems came together, there was a semicircular scale, also made of aluminum. The scale had marks ranging from 2-10 cm at 2-cm intervals, and it was fastened to the stems by three screws and three brass washers to allow opening and closing of the stems. Measurements that had been previously obtained were classified as < 6 cm and > 6 cm. Two patients were in the < 6 cm category prior to treatment, and all others had a cervix measuring over 6 cm in diameter. Six patients had tumors in Stage IB, three in Stage IIA, nine in Stage IIB, two in Stage IIIA, and seven in Stage IIIB. Most patients (24) had epidermoid carcinoma; the remaining three were diagnosed with adenocarcinoma.

The chemotherapeutic scheme herein proposed as a neoadjuvant consisted of at least three courses and at most five courses lasting one day each. There were four to six week intervals between the courses. The scheme follows below: bleomycin: 30 mg/m^2 in intravenous infusion with physiological saline solution for two hours; methotrexate: 50 mg/m^2 in intravenous bolus given immediately after the administration of bleomycin; mitomycin C: 20 mg in intravenous bolus given at the end of the course. Each course was followed by colposcopy, oncologic cytology, and lab exams. The third course was also followed by thoracic X-ray and, when necessary, excretory urography.

Statistical analysis

Responses were categorized as complete response (CR; total regression of the tumor), partial response (PR; regression of the cervix diameter was equal to or greater than 50% of the initial measurement), stable disease (SD; regression of the cervix diameter was less than 50% of its initial measurement), progressive disease (PD; the cervix diameter lengthened).

Descriptions of the observed toxic effects and their consequences, if any, as well as abnormalities in the radiological and lab exams at the end of treatment programs were included.

Results

There was an objective response in 81.4% of the cases (16 complete responses and 6 partial responses). The disease stabilized toward the end of treatment in the other five patients. No cases of progressive disease were found.

Table 1. — *Association between treatment responses and clinical observations prior to treatment, involvement of parametria, clinical stages, histological types and degrees, and cervical diameter prior to therapeutic program.*

Parameters	Objective Response		No Response	
	Number of patients	%	Number of patients	%
Clinical observations				
Tumor restricted to cervix	17/19	89.47	2/19	10.53
Cervical + vaginal tumor	5/8	63.00	3/8	37.00
Involvement of the parametria				
Right	6/7	85.71	1/7	14.29
Left	3/4	75.00	1/4	25.00
Right + Left	4/5	80.00	1/5	20.00
Free	9/11	81.82	2/11	18.18
Clinical Stages				
IA	6/6	100.00	0	0
IIA	2/3	66.67	1/3	33.33
IIB	9/9	100.00	0	0
IIIA	½	50.00	1/2	50.00
IIIB	4/7	57.14	3/7	42.86
Histological types				
Epidermoid	19/24	79.17	5/24	20.83
Adenocarcinoma	3/3	100.00	0	0
Histological degrees				
I	3/3	100.00	0	0
II	10/12	83.33	2/12	16.67
III	9/12	75.00	3/12	25.0
Cervical diameter prior to treatment				
> 6 cm	20/25	80.00	5/25	20.0
< 6 cm	2/2	100.00	0	0

Thirteen patients presented adverse reactions, mostly nausea, vomiting (50%) and altered values of hemoglobin and leucopenia (50%). These reactions did not limit the application of the proposed treatment. Five patients (18.5%) suffered from discrete alopecia, and one patient had injection-site necrosis resulting from overflow of mitomycin C.

Table 1 shows the values of the objective response with respect to the clinical observations prior to treatment, involvement of parametria, clinical stages, type and histological degree of tumor, and uterine cervix diameter before administration of the therapeutic scheme. All patients who responded objectively to chemotherapy underwent complementary treatment (surgery and/or radiotherapy) and are alive with no evidence of the disease after 15 years of follow-up. In fact, three patients have died up now due to cardiovascular disease.

Discussion

Diverse clinical studies give evidence of the value and efficacy of neoadjuvant chemotherapeutic schemes for the treatment of uterine cervix carcinoma, emphasizing benefits such as the early treatment of systemic micro metastases, reduction of primary tumor size, and enhanced possibility of surgical and/or radiotherapeutic complementation [13, 14]. This study showed that the combination of mitomycin C, bleomycin and methotrexate was effective and had no serious side-effects. Also,

more radical therapeutic complementation following chemotherapy was beneficial for the patients.

Chemotherapy as a first-rate treatment for advanced uterine cervical carcinoma was first suggested by Friedlander *et al*. [15] and shortly afterwards by Kim *et al*. [16]. Those studies were an important step forward not only in the treatment of this type of cancer but also in the role of chemotherapy. The reported responses were 67% and 100% when using a scheme that included cisplatin, vinblastine and bleomycin. As the use of neoadjuvant chemotherapy expanded, patients with tumors previously considered to be inoperable were able to undergo successful surgery after chemotherapy [13-16].

Most schemes utilized in neoadjuvant chemotherapy are based on combinations of agents that include cisplatin, and the objective responses to these treatments are in the 60%-100% range [15-17]. None of the previous studies have reported serious toxicity, although severe myelosuppression was observed by Rustin *et al*. [17], while Kim *et al*. [16] had to modify the dosage due to serious neutropenia.

Finally, our research suggests that better histological differentiation of tumors can increase the chance of a response to the proposed treatment. We therefore believe that the proposed neoadjuvant chemotherapeutic treatment might be an alternative for women with uterine cervical carcinoma, as it improves the indication for surgery and/or radiotherapy as a follow-up treatment without serious adverse effects.

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