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Ifosfamide and mesna at high doses for the treatment of cancer of the cervix: a GETLAC study **

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Summary. This study was carried out to assess the efficacy of high-dose ifosfamide/mesna (HDIFM) in the treatment of advanced or recurrent cancer of the cervix. In all, 18/21 evaluable patients with advanced or inoperable cervical cancer were included. The mean age was 42 years (range, 31–58 years); and the International Federation of Gynecology and Obstetrics (FIGO) stage was III in 10 patients and IV in 11. The Karnofsky performance status ranged between 70 and 90, with a median of 77. Ten patients had previously been treated with surgery, radium and cobalt (8) or cobalt alone (2). Therapy consisted of 3.5 g/m^2, ifosfamide (IFO) given in an 8-h i.v. infusion on days 1–5 and mesna at 20% of the IFO dose, given i.v. at 0, 2, 4, 6 and 8 h, followed by mesna at 40% of the IFO dose by the oral route at 10 and 12 h on days 1–5. For evaluation purposes, patients received at least two cycles. Toxicity was registered in 137 cycles and was mild to moderate. Three complete (16.6%) and six partial (33.3%) responses were observed (50%), but 66% of them occurred in areas that had not previously been irradiated. The median duration of response was 14 months and the overall median survival was 15+ months (18+ months for responders). The Karnofsky scale after treatment ranged from 90 to 100. The results of this study indicate that HDIFM is well tolerated, giving a high percentage of remission (50%) and significantly improving the quality of life.

Introduction

For cervical cancer of stages III and IV, radical radiotherapy offers a sub-optimal therapeutic approach; extensive tissue necrosis and post-radiation fibrosis may interfere with chemotherapy access and complicate evaluation of local therapeutic responses. Traditionally, chemotherapy has been reserved for palliation of local recurrences or metastatic cervical cancer, resulting in responses of short duration. The frequency of response of squamous-cell carcinoma of the cervix has been distressingly low for single-agent chemotherapy [13].

Ifosfamide (IFO) is a structural analogue of cyclophosphamide and belongs to a type of cancer chemotherapeutic agents known as oxazaphosphorine nitrogen mustard [1]. Hematuria and cystitis, the dose-limiting toxicity caused by acrolein and additional IFO metabolites, can be neutralized by concurrent sodium-2-mercaptoethanesulphonate (mesna) given by the i.v. and/or oral route; mesna interacts with acrolein and other IFO metabolites and prevents damage to the bladder mucosa. IFO is one of the most active single drugs for advanced cancer of the cervix. The best response rates that have been reported for this drug range from 20% to 40% and may vary with the dose and frequency of administration [6, 7, 11].

This paper reports our experience at the Hospital Municipal of Vicente López with the administration of high doses of IFO/mesna (HDIFM) in patients with recurrent or metastatic squamous-cell carcinoma of the uterine cervix to test the efficacy of IFO, the improvement in survival and quality of life, and the tolerance of high doses.

Patients and methods

Patients with recurrent or metastatic epidermoid squamous-cell carcinoma of the cervix (mean age, 42 years; range, 31–58 years) were entered in this study if they had disease parameters measurable by physical examination, roentgenographic studies, radioisotopic scans, ultrasound scans, and/or computerized tomographic studies. The treatment observations also included a complete history and physical examination

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Table 1. Patient characteristics

Patients entered	21
Age	42.9 (range, 31–59) years
Median Karnofsky performance status	80% (range, 70%–90%)
Initial stage III	10
Initial stage IV	11
Previous treatment:	
None	11
Surgery + radium + cobalt 60	2
Cobalt 60	8
Metastases	6
Weight loss	16

Table 2. Response to HDIFM in patients with stage III–IV cancer of the cervix

Previous treatment	Patients	Response: CR	PR	NC	PD	Non-evaluable
None	11	2	4	3	2	0
Radical hysterectomy + radium + cobalt 60	8	0	2	2	2	2
Cobalt 60	2	1	0	0	0	1
Totals	21	3	6	5	4	3

with base-line laboratory studies. Patients were seen weekly/every 2 weeks, with a follow-up physical examination and repeated laboratory studies at 1- to 2-week intervals for response and toxicity monitoring (Table 1).

The following eligibility criteria were used to determine admission to the study: initial presentation with advanced cervical cancer, histological documentation of squamous-cell carcinoma, a Karnofsky index of >60, adequate renal function, adequate hepatic and bone marrow functions, and a minimal life expectancy of ≥ 8 weeks.

Prior to entry in the study, patients were stratified according to prior anti-cancer therapy. Each cycle of treatment consisted of 3,500 mg/m^2 IFO given as an 8-h i.v. infusion on days 1–5 and 700 mg/m^2 mesna given by i.v. push at 0, 2, 4, 6 and 8 h, followed by 1,400 mg/m^2 mesna given by the oral route at 10 and 12 h on days 1–5. Cycles were repeated every 4 weeks for 8 consecutive cycles of treatment. Patients were evaluated at monthly intervals and after the completion of eight cycles. Hematological, renal and liver functions were monitored in the usual way.

A complete response (CR) was defined as the complete disappearance of all known disease as determined by two observations at least 4 weeks apart. A partial response (PR) required a decrease of at least 50% in the total tumor size without the appearance of new lesions. No change (NC) or stable disease was indicated when a 50% decrease in the total tumor size could not be established or a 25% increase could not be demonstrated. Progressive disease (PD) was indicated by an increase of $\geq 25\%$ in the size of more than one lesion or the appearance of new lesions.

Results

In all, 18 of 21 evaluable patients with advanced or recurrent cervical cancer were available for evaluation. Eight patients had previously received a full course of radical radiotherapy. In all, three CRs (16.6%) and six PRs (33.3%) were observed (50%) (Table 2). The median duration of response was 14+ months (range, 4–16+ months). Three patients died. The median survival for CRs was 19+ months (range, 18–23+ months); that for PRs was 16+ months vs 14 months for non-responders. Overall, 15 patients are still alive, including all of the responders; the median overall survival is 15+ months.

Toxic effects were registered for all 21 patients, who received a total of 137 cycles of treatment. In all patients alopecia and nausea and vomiting were noted. No impairment of renal function occurred. However, microscopic hematuria was observed in three patients and cystitis was seen in two cases. Hematological toxicity was infrequent and usually mild: three patients had a WBC count nadir of <3,000/mm^3. None of our patients had a platelet count nadir of <90,000/mm^3, but hemoglobin values of <10 g/dl were noticed in three patients. CNS symptoms (mild leucoencephalopathy) lasting 30 h were registered in one patient. Weakness of the legs was reported in five patients. There were no deaths due to chemotherapy.

Discussion

For many reasons, chemotherapy has been neglected in the treatment of recurrent, advanced or metastatic squamous-cell carcinoma of the cervix. The problems associated with the administration of cytostatics and those related to previous irradiation, namely, obstructive uropathy, infection and general weakness, have militated against their use. Patients included in these trials had a high Karnofsky index, apparently as an important prognostic factor.

Response rates for single-agent chemotherapy have generally been based on trials in patients who had received extensive prior chemotherapy as well as radiotherapy. Chemotherapeutic responses in recurrent cervical carcinoma have previously been reported at 10%–40% for single agents [10] and at up to 90% for multiple therapy regimens [3]. More recently, higher frequencies of response have been reported, but the duration of response has still been relatively short, with little survival benefit. Because of this relative lack of success in cervical carcinoma, the the GETLAC undertook this study of IFO/mesna as first-line chemotherapy in advanced disease, in an effort to identify agents with a high rate of activity. IFO was selected based on a report of 1 CR and 9 PRs among 30 patients with no prior chemotherapy who were given a dose of 5 g/m^2 every 3 weeks [11]. A dose of 3,500 mg/m^2 daily for 5 consecutive days (17.5 g/m^2) was selected because of evidence of a dose-response relationship with IFO [4, 5].

Evidence of a high index of efficacy is shown for IFO/mesna in squamous-cell carcinoma of the cervix when the drug is used as a first-line agent. Our observation of 9 objective responses among 18 evaluable patients confirms the report of Meanwell et al. [12]. Furthermore, the median response duration of 14 months exceeded that reported for other regimens, as did the median survival of 19 months. The drug appears to be effective in reducing pelvic as well as extra-pelvic disease. The objective response in

ten previously irradiated areas was about 33%, but response rates in non-irradiated sites of disease amounted to 66% (Table 2).

IFO has a long serum half-life; after the termination of IFO infusion, there are still considerable serum concentrations of 4-hydroxyifosfamide, the major cytocidal metabolite of IFO. On the other hand, the excretion of mesna slows down very rapidly after the end of mesna infusion [8, 9]. A daily dose of 3,500 mg/m^2 IFO given as a long-term, 8-h i.v. infusion was less toxic than single-push injections, because high peak serum concentrations were avoided. Moreover, at the end of treatment, better tolerability and higher therapeutic efficacy were achieved, compared with those obtained using a single-push injection.

The control of dose-limiting urotoxicity was ensured in this trial by giving higher and repeated doses of mesna by both the i.v. and oral routes [2]. The mean IFO dose of 17,500 mg/m^2 per cycle was accounted for by giving seven consecutive daily doses of mesna in an IFO/mesna dose relationship of 1 : 1.8 (mg/m^2 basis).

Adverse effects in this study population were tolerable, with no drug-related deaths noted. Myelosuppression was mild to moderate. Perhaps most unpleasant from the patient's point of view was gastrointestinal toxicity; nausea and vomiting were virtually universal despite a variety of measures attempting to suppress gastrointestinal upset. Nephrotoxicity was not seen in this trial. After 137 cycles of HDIFM chemotherapy, dose-limiting side effects such as cardiac dysrhythmias and macrohematuria were not reported. Microhematuria was observed in three cycles (4.1%), and reversible CNS disturbances were noted in only one patient.

The efficacy of this chemotherapy can be attributed to: (1) an increased daily dose of IFO (median total dose/cycle, 17.5 g/m^2), associated with a new modality for mesna administration, improving the control of urotoxicity; (2) mild toxicity with excellent tolerance; (3) a good Karnofsky index for patients entered in the study; and (4) no previous chemotherapy.

IFO/mesna is clearly active in the therapy of squamous-cell carcinoma of the cervix. A response rate as high as 50% could be achieved following eight courses of HDIFM chemotherapy, with manageable associated toxicity. The therapy could safely be given on an out-patient basis, with encouraging improvement of patients' quality of life.

In conclusion, these results suggest that HDIFM is a useful regime for palliation of advanced and recurrent cervical cancer. Further studies are needed to identify other active agents that may logically be combined with HDIFM to produce more frequent and longer-lasting responses.

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