Original Article

Drug Management Pattern and Their Adverse Effects in Patients of Cervical Carcinoma Attending Two Tertiary Care Hospitals in Dhaka City

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Abstract

***Background**: Cervical cancer remains a significant health burden worldwide. It is the second most commonly diagnosed cancer and third leading cause of cancer death among females in least developed countries. There were an estimated 527,600 new cervical cancer cases and 265,700 deaths worldwide in 2012. Bangladesh stands 11th in the world in cervical cancer fatalities with 17.9 women dying in 100,000 due to the largely sexually transmitted disease every year. **Objective**: The present study was done to evaluate the pattern of drug management, their adverse effects and socio-demographic characteristics of the patients of cervical carcinoma admitted and treated with chemotherapy in two tertiary care hospitals of Bangladesh. **Materials and Methods**: It was a cross-sectional observational study carried out from January to December 2015 at Dhaka Medical College & Hospital and National Institute of Cancer Research Hospital. During this period, 109 patients were selected by purposive sampling technique using a set of pre-tested structured questionnaire. Data analysis was done using SPSS version 21.0. **Results**: Most of the patients were in 5th decade (51.4%), from low (59.6%) income family and were married (98.16%). The mean duration of treatment for cancer was found 11.34 ± 5.32 months. Cisplatin (93.57%), 5 fluorouracil (63.3%) and paclitaxel (12.8%) were the most frequently prescribed drugs either alone or in combination. The adverse effects for cisplatin were gastrointestinal toxicity, nephrotoxicity, myelosuppresion and for 5-fluorouracil were myelosuppression, diarrhea, hyperpigmentation, dizziness, neuropathy, increased risk of infection. **Conclusion**: The combination of cisplatin and 5-fluorouracil was mostly (50.45%) prescribed followed by cisplatin alone (26.6%) to treat the patients of cervical carcinoma in Bangladesh.*

***Key words**: Cervical carcinoma; Chemotherapeutic agents; Adverse effects of chemotherapy; Cisplatin; 5-Fluorouracil*

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Introduction

Cervical cancer is one of the commonest cancers in women with high mortality rate. Here cervical cells go through dysplasia, in which abnormal cells grow and spread deeply into the cervix and surrounding areas. Human papilloma virus **(**HPV**)** infection is the major risk factor for cervical cancer.[1-3] Eighty percent of cervical cancer of the globe occurs in the developing countries.[4]

In 2000 the number of patients diagnosed with cervical carcinoma and those who died from cervical cancer were 470,606 and 233,372 respectively.[5] There were an estimated 527,600 new cervical cancer cases and 265,700 deaths worldwide in 2012. It is the second most commonly diagnosed cancer and third leading cause of cancer death in least developed countries.[6] The high rate of mortality is remarkable although cervical cancer is a model for early detection due to its long natural history that offers an excellent opportunity for its detection before lesions become invasive.[7]

Incidence rates are highest in sub-Saharan Africa,

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Latin America, the Caribbeans and Melanesia and lowest in Western Asia, Australia, New Zealand and Northern America. Nearly 90% of cervical cancer deaths occurred in developing parts of the world: 60,100 deaths in Africa, 28,600 in Latin America and the Caribbeans, and 144,400 in Asia. India accounted for 67,500 (25%) of cervical cancer deaths.[6] The large geographic variation reflects differences in the availability of screening which allows for the detection of cervical cancer. It is important that all women, even those who have been vaccinated, should be screened, because HPV vaccines cannot protect against established infections, or all of the types of HPV. The most efficient and cost-effective screening techniques in low-resource countries include visual inspection using acetic acid and HPV tests.[8] A clinical trial in rural India found that a single round of HPV testing reduced the number of cervical cancer deaths by about 50%.[9] The treatment of cervical cancer varies with the stage of the disease. Globally, the majority of cancers are locally advanced at diagnosis; hence radiation remains the most frequently used therapeutic modality. Currently, the addition of cisplatin or cisplatin-based chemotherapy to radiation (CCRT) for locally advanced cervical cancer is hugely practiced. The theoretical advantages of CCRT were that the chemotherapy agent might be effective in eradicating the subclinical metastasis and act as a radiosensitizer.[10] The chemotherapy drugs used for CCRT were cisplatin, 5-fluorouracil, hydroxyurea, ifosfamide, mitomycin-C and bleomycin.[11] In the late 1990s, five randomized prospective studies reported the superiority of CCRT to radiation alone in the treatment of locally advanced or high-risk cervical cancer.[12,16]

There have been many studies on the combination use of 5-FU and cisplatin in patients with cervical cancer.[17,18] Cisplatin acts synergistically with the radiation by killing the cells with radiation-induced sublethal damage.[19] 5-Fluorouracil exhibits the synergistic effect with radiation by inhibiting the DNA replication in cells which are damaged by radiation.[20]

Stage IA, IA2, IBI and IIA can be treated by surgery, with or without radiation therapy. For stage IIB, III, or IVA, cisplatin and 5-fluorouracil-based chemotherapy with radiation is the standard treatment for carcinoma. For stage IVB and recurrent cancer, individualized therapy is used on a palliative basis; radiation therapy is used alone for control of bleeding and pain; systemic chemotherapy is used for disseminated disease.[21] In Bangladesh several combinations of chemotherapy are used as neoadjuvant or adjuvant therapy with or without radiation by individualization of patients.[22]

Drugs used in different chemotherapy protocol for cervical cancer[23] are cisplatin, carboplatin, paclitaxel, docetaxel, 5-fluorouracil, gemcitabine, bevacizumab, bleomycine, ifosfamide, vinorelbine, irinotecan**,** pemetrexed.

Chemotherapy destroys cancer cells, but it can also harm healthy cells that may cause side-effects, but often these get better or go away after chemotherapy is over.[24] Common side-effects of any chemotherapy are fatigue, nausea and vomiting, hair loss, increased risk of infection, bruising and bleeding, mouth sores, loss of appetite, changes in skin and nails, problem with memory, concentration and sleep, diarrhea, constipation, etc.[25] Cisplatin-based adverse effects are nephrotoxicity, upper gastrointestinal toxicity, and myelosuppression[19] and for 5-FU these are myelotoxocity, diarrhea, dizziness and hyperpigmentation[20] .

This study aimed to evaluate the pattern of drug management, their adverse effects and socio-demographic characteristics of the patients of cervical carcinoma admitted and treated with chemotherapy in two tertiary care hospitals of Bangladesh.

Materials and Methods

This cross-sectional observational study was carried out among the patients diagnosed as cervical carcinoma and getting chemotherapy. The period of study was January to December 2015. Data were collected from Dhaka Medical College & Hospital (DMCH) and National Institute of Cancer Research Hospital (NICRH). The study population consisted of 109 patients. The subjects were selected by purposive sampling technique. Diagnosed case of cervical carcinoma and patients who gave consent for the study were included. Pregnant, severely ill and patients with other concomitant illness were excluded from the

study. Adverse effects of different chemotherapeutic agents were evaluated. Gastrointestinal toxicity was evaluated by severity of nausea, vomiting, diarrhea, level of bilirubin and liver enzymes. Myelotoxicity was evaluated by the level of hemoglobin, white blood cell and platelet count. Nephrotoxity was evaluated by the level of serum creatinine. Data were collected by a face to face interview by using a set of pretested structured questionnaire. The prescriptions of the patients were reviewed. Data analysis was done using SPSS version 21.0.

Results

The mean age of the subjects was 49.72 ± 8.22 years. Among the subjects 65 (59.6%) patients came from low economic group and 43 (39.4%) from middle income group. Most of the patients (107, 98.16%) were married. The mean duration of treatment for cancer was found 11.34 ± 5.32 months, total number of drugs prescribed were 1.76 ± 0.49 (Table I). Different chemotherapeutics prescribed to patients are shown in Table II. Fifty five (50.45%) patients were treated by combination of cisplatin and 5-fluorouracil, 29 (26.6%) with cisplatin alone, 14 (12.8%) with combination of cisplatin, 5-flurouracil and paclitaxel, 6 (5.5%) with carboplatin alone, 2 (1.83%) with combination of cyclophosphamide and cisplatin, 2 (1.83%) with doxorubicin and cisplatin, and doxorubicin alone was used in 1 (0.9%) patient. Patients receiving any chemotherapeutic agents commonly suffered from nausea, vomiting, loss of hair, loss of appetite, mucositis, diarrhoea and constipation. Common toxicities for cisplatin were nephrotoxicity, upper gastrointestinal toxicity and myelosuppression. Hyperpigmentation, dizziness, neuropathy, diarrhea were experienced by patients who received 5-fluorouracil. Paclitaxel caused neuropathy, hyperpigmentation, flushing, burning of limbs, anemia, constipation, muscle and joint pain, numbness of hands and skin rash. For doxorubicin, increased risk of infections, bone pain, hyperpigmentation, amenorrhea, anemia, diarrhea and allergy were common. Carboplatin frequently caused nausea, vomiting, loss of hair, neuropathy, bone pain and weakness. Adverse effects of different chemotherapeutic agents are shown in Fig 1.

Table I: Baseline characteristics of study population (N=109)

Variables	Values
Number of patients	109
Age (in years)	49.72 ± 8.22
Socio-economic status a. Low b. Middle	 65 (59.6%) 43 (39.4 %)
Duration of treatment (in months)	11.34 ± 5.32
Total number of drugs prescribed	1.76 ± 0.49

Table II: Different chemotherapeutics prescribed to patients (N=109)

Drugs	Number	Percentage
Cisplatin + 5-fluorouracil	55	50.46
Cisplatin	29	26.61
Cisplatin + 5-fluorouracil + paclitaxel	14	12.84
Carboplatin	06	5.50
Cisplatin + cyclophosphamide	02	1.83
Cisplatin + doxorubicin	02	1.83
Doxorubicin	01	0.92

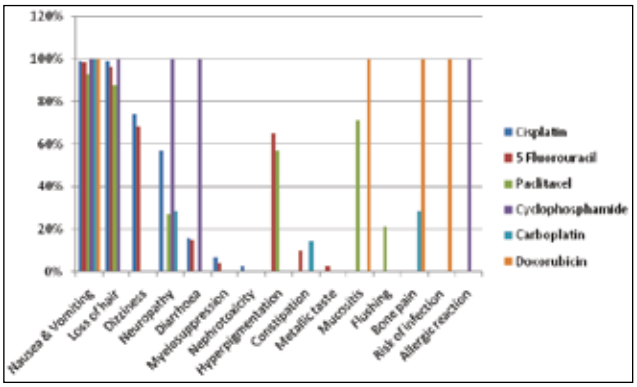

Fig 1. Adverse effects of different chemotherapeutic agents

Discussion

In this study 56 (51.4%) patients were in the 5th decade with mean age 49.72 ± 8.22 years. Similar findings were observed by other studies.[5,12,26] Majority of the patients (59.6%) came from low income group and 98.16% were married. These findings are consistent with some other studies.[12,18,27] In the current study 50.9% patients got treatment for 6−10 months

with mean duration of 11.34 ± 5.32 months, 87.2% received treatment with ≤2 drugs and mean total number of drugs prescribed was found 1.76 ± 0.49. Findings are consistent with that of other studies.[27,28] In this study majority (102, 93.57%) of the patients received cisplatin followed by 5-flurouracil (69, 63.3%) and paclitaxel (14, 12.8%). Fifty five (50.46%) patients were treated by combination of cisplatin and 5-flurouracil and it is consistent with some previous studies.[29,30]

Paclitaxel is mostly used in the treatment of several types of cancer, either alone or in combination because of its effectiveness in wide range of tumors.[31] In this study paclitaxel caused nausea and vomiting (92.9%), loss of hair (87.6%), mucositis (71.4%), neuropathy (27.1%), hyperpigmentation (57.1%) and flushing (21.4%). Burning of limbs, anemia, constipation, muscle and joint pain, numbness of hands and skin rash were experienced by few patients.

Side effects of platinum therapy include nausea and vomiting, myelosuppresion, immunosuppression, nephrotoxicity, neurotoxicity and hearing loss.[32-36] In this study patients who were treated by cisplatin experienced nausea and vomiting (99%), loss of hair (99%), dizziness (73.9%), neuropathy (57.2%), diarrhea (15.9%), myelosuppression (6.87%) and nephrotoxicity (2.7%). Carboplatin was given in six patients. All of them developed nausea, vomiting and loss of hair. Peripheral neuropathy was present in 2 (28.6%) patients, weakness and constipation in 1 (14.3%) and bone pain was present in 2 (28.6%) patients.

In this study, after receiving 5-flurouracil and paclitaxel, the most common findings were nausea and vomiting (98.2%), loss of hair (98.2%), loss of appetite (89.9%), mucositis (75.2%), numbness of hands (56.0%), dizziness (69.7%) whereas hyperpigmentation, anemia, bone pain and diarrhea were frequently found. Neuropathy, flushing and burning of limbs were experienced by a few number of patients. In another study after receiving 5-flurouracil and paclitaxel most common adverse drug reactions (ADRs) were nausea and vomiting (85.45%), loss of appetite (72.72%), mucositis (65.45%), pain (63.63%), dyspnea (40.0%), constipation (52.72%) and polyneuropathy (58.18%).[31]

In this study 69 patients received 5-flurouracil. Nausea and vomiting (98.6%), loss of hair (96.4%), dizziness (68.6%) and hyperpigmentation (65.2%) were commonly found. Diarrhea (14.8%), constipation (10.1%), myelosuppression (3.84) and metallic test (2.9%) were experienced by few patients.

Cyclophosphamide was prescribed in only one patient. Nausea and vomiting, loss of hair, allergic reaction, neuropathy and diarrhea were most commonly found adverse effects. Doxorubicin was received by only one patient. Nausea and vomiting, mucositis, loss of hair, increased risk of infection and bone pain were commonly found. Similar results were observed in another studiy.[37]

This study has some limitations. Study population was selected from two hospitals in Dhaka city, and the study was conducted in a short period of time with a small sample size. So the results of the study may not reflect the exact picture of the whole country. Treatment delays, deviations from standard dosing by body surface area or other parameters and use of ancillary medications were not evaluated. These questions are key priorities for future research.

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