THAI JOURNAL OF PHYSIOLOGICAL SCIENCES
Volume 17 (No.3, December 2004)
Page 90-97
www.tjps.org
ISSN 0857 – 5754

Original Article

ACUTE TOXICITY OF CONCOMITANT TREATMENT OF CHEMORADIATION WITH SINGLE AGENT CISPLATIN IN PATIENTS WITH CARCINOMA OF THE CERVIX

V.M.K. Bhavaraju[1], N.S. Reed[2], and T. Habeshaw[3]

[1]Deparment of Nuclear Medicine, Radiotherapy, and Oncology, Universiti Sains Malaysia, Kubang Kerian, 16150, Kelantan, Malaysia, [2]Beatson Oncology Centre, Glasgow, Scotland, United Kingdom, and. [3]Roche Pharmaceuticals

This study assessed the acute toxicity that results from simultaneous chemoradiotherapy with cisplatin and radiation therapy in patients with carcinoma of the cervix. Thirty-five patients with carcinoma of the cervix at all stages were selected from the Beatson Oncology Centre, Glasgow, Scotland. Patients were treated for 4 - 6 weeks with weekly infusion of cisplatin and external beam radiotherapy. Twenty-six of the 35 patients (74.3%) were diagnosed with stage II and III tumors (Federation International de Gynecologie de Obstetrique; FIGO). The major adverse toxic responses identified were hematological toxicity (anemia 62.9%, neutropenia 51.4%, and thrombocytopenia 17.1%), gastrointestinal toxicity (nausea and vomiting 65.7% and diarrhea 54.4%), skin changes, fatigue and oto toxicity. Other than hyponatremia (22.9%), no electrolyte disturbances, e.g., hypomagnesaemia or hypokelemia, were found to be associated with the therapy. Eight patients (22.8%) had unplanned admission to hospital during the treatment. Concurrent chemotherapy with cisplatin 40 mg/m^2 weekly along with radiotherapy was well tolerated by the patients. The adverse toxicity was mild and manageable. Thus, chemoradiotherapy with cisplatin does not have major adverse effects in patients with locally advanced carcinoma of the cervix.

Key words: cisplatin, chemoradiotherapy, radiation therapy, cervical carcinoma

Cancer of the cervix is one of the most common gynecological cancers and remains a major health problem worldwide (Cellini et al., 2002; Rose, 2000), with an estimated 750,000 new cases annually (International network meeting, Brussels, 2001). While the incidence of carcinoma of cervix has been decreasing in developed countries, it remains the third most common cancer-affecting women (Parkin et al., 1999). In 2000, about 500,000 patients were diagnosed with carcinoma of cervix and 233,372 deaths from it were recorded (Duenas–Gonzalez et al., 2003; Parkin et al., 2001). In the developing world, carcinoma of the cervix is still a leading form of cancer (Cellini et al., 2002) and patients tend to be treated only at advanced stages of the disease (Duenas-Gonzalez et al., 2003).

Recent development in the treatment of cervical cancer has extended the survival of

Received: October 6, 2004; accepted: November 30, 2004
Correspondence should be addressed to Dr. V.M.K. Bhavaraju, Department of Nuclear Medicine, Radiotherapy, and Oncology, Universiti Sains Malaysia, Kubang Kerian 16150, Kelantan, Malaysia. @mail: drmurali@kb.usm.my

these patients (Duenas-Gonzalez et al., 2003), and novel techniques in surgery, radiotherapy chemotherapy and a combination-treatment approach promise to increase the survival rates even more (Greentee et al., 2001). Nonetheless, the management of locally advanced cancer of cervix has not experienced significant change over the last 80 years and radiotherapy is still the gold standard (Duenas-Gonzalez et al., 2003). Such technical innovations such as hyperthermia (Hornback et al., 1986), neutron beam irradiation (Maor et al., 1988), interstitial brachytherapy (Monk et al., 1997), and high dose rate intra-cavity brachytherapy (Stitt et al., 1992) have not had a significant beneficial impact on this survival. In the late 1970s, the Gynecology Oncology Group (GOG) attempted to use the combination of chemotherapy with radiotherapy in patients of carcinoma of the cervix. The first randomized phase III trial with hydroxyurea plus radiotherapy versus radiotherapy alone-demonstrated significant improvement in the survival rates (Hershchysyn et al., 1979).

Most of the studies have focused on the application of a wide range of chemotherapeutic agents in order to improve the survival rates of patients with cancer of the cervix. The most commonly used anticancer drugs are hydroxyurea (Hershchysyn et al., 1979), 5-fluorouracil (Whitney et al., 1999), mitomycin-c (Lorvidhaya et al., 2003), cisplatin (Keys et al., 1999), epirubicin and newer drugs like gemcitabine and paclitaxel. Studies report significant increase in the survival rates in patients when chemoradiotherapy with weekly prescription of cisplatin concomitantly. Based on the evidence from these studies, the National Cancer Institute (NCI) issued a global clinical recommendation for the use of chemoradiotherapy approach in patients with cervical cancer (United States Department of Health & Human Services, 1999).

However, chemoradiotherapy and radiation are associated with significantly increased morbidity. Hence, it is important to systematically define the adverse effects of these treatments. The present study assessed the toxicity of chemoradiotherapy cisplatin in 35 cervical carcinoma patients.

Material and Methods

Thirty-five patients with cervical carcinoma (all stages) were treated with weekly infusion of cisplatin along with irradiation of the whole pelvis. The patient's characteristics were given in Table 1.

Table 1. General characteristics of the patients

Parameters	Number of patients	Distribution (%)
Age (years)		
<30	2	5.7
31.40	9	25.7
41-50	12	34.3
51-60	6	17.1
61-70	6	17.1
Stage of carcinoma		
I	4	11.4
II	16	45.7
III	10	28.6
IV	5	14.3

All of the patients were biopsy confirmed for cervical cancer and were investigated with full blood counts and renal function tests to assess the baseline status of the bone marrow and kidney function. A postero-anterior view chest X-ray was done in all the patients to rule out metastasis of the lungs. Informed written consent was taken from all the patients prior to chemoradiation.

These patients were planned for external radiation with the linear accelerator to the whole pelvis followed by intracavitary insertion after external radiation. The technique used was a four field brick to the pelvis, treating all the fields daily with a dose of 43Gy in 20 fractions over 28 days followed by single intra-cavitary insertion with MDR selectron to give 26Gy to point A. Patients received injection cisplatin 40mg/m^2 weekly along with radiation. The aim was to administer up to six doses of cisplatin weekly.

The patients were evaluated for complications using the Common Toxicity Criteria (CTC) of the National Cancer Institute (CTC NCI, 1999) for gastrointestinal (GI), renal, hematological, and skin parameters. Interruptions during the treatment protocol and the unplanned admissions were analyzed.

Each patient was analyzed by full blood count and renal function test weekly prior to chemotherapy to assess the hematological and renal status. A weekly physical assessment and examination conducted on these patients (NSR and TH).

The hematological toxicity assessed in the form of changes in hemoglobin percentage, leukocyte and platelet counts. The renal toxicity was assessed by the estimation of serum creatnine level, blood urea level, and serum electrolytes.

Results

All the patients (except one) received 4-6 cycles of weekly cisplatin 40mgs/m^2 during radiotherapy. One patient received only 2 cycles of chemotherapy. The toxicity profiles of these patients were given in Table 2.

Hematological toxicity

Patients with hemoglobin levels less than 10 g/dl were considered anemic and they received blood transfusion for correction of anemia. We have subsequently aimed for a target level of 12 g/dl. Hemoglobin toxicity grade I was detected in 51.5% of patients, and grade II was present in 11.4% of patients. Severe toxicity was not present in grade III and IV patients.

Leukocyte counts were highly variable. Sub-analysis demonstrated that patients had leucopenia in the 4^{th} – 6^{th} week of chemotherapy. Eighteen of 35 patients (51.4%) developed leucopenia (grade I 20% and grade II 31.4%). In contrast to Straus, (Strauss et al., 2002), we did not detect leucopenia in grade III patients. Thrombocyte counts displayed less variation between subjects. Thrombocytopenia was present in 6 patients (17.1%). Out of these patients, only one was grade I. (Table 2).

Renal toxicity

Among the 35 patients studied, two patients (5.7%) showed changes in the blood urea levels. Changes in the serum creatnine level on the higher side were noted in five patients (14.3%). The normal values of blood urea 6.7 mmol/l and serum creatnine 130 mmol/l were the baseline cutoffs for the evaluation of toxicity.

Among the serum electrolytes, serum sodium displayed decreased trends during the chemoradiotherapy. We did not observe any hypomagnesemia or hypokelemia as in other studies using cisplatin-based chemotherapy (Al-Tweigeri et al., 1999; Lajer and Daugaard, 1999; Li et al., 1995). Hyponatremia noted in 22.9% of patients during the week 3-5 of chemotherapy.

Table 2. Hematological, gastrointestinal, and skin toxicities of combined treatment

Parameters	Number of patients	Distribution (%)
Hematological toxicity		
Grade 0	13	37.1
Grade I	18	51.5
Grade II	4	11.4
Grade III	0	0
Grade IV	0	0
Neutropenia		
Grade 0	17	48.6
Grade I	7	20
Grade II	11	31.4
Grade III	0	0
Grade IV	0	0
Platelets		
Grade 0	29	82.9
Grade I	5	14.3
Grade II	1	2.8
Grade III	0	0
Grade IV	0	0
N**ausea and vomiting**		
Grade 0	12	34.3
Grade I	3	8.6
Grade II	12	34.3
Grade III	7	20.0
Grade IV	1	2.8
Diarrhea		
Grade 0	16	45.6
Grade I	8	22.9
Grade II	8	22.9
Grade III	3	8.6
Grade IV	0	0
Skin toxicity		
Grade 0	33	94.3
Grade I	1	2.8
Grade II	1	2.8
Grade III	0	0
Grade IV	0	0

Other toxicities

We have noted slightly higher hyponatremia than others (Payrade et al., 1997).

Gastro intestinal (GI) toxicity

Chemoradiotherapy was well tolerated by these patients; however, the GI toxicity symptoms such as nausea, vomiting, and diarrhea were evident (Table 2). GI toxicity was graded according to the common toxicity criteria of National Cancer Institute. Nausea and vomiting were noted in 23 patients (65.7%). Most patients reported grade I or II diarrhea (22.9% each). Three patients (8.6%) had grade III diarrhea. These toxicity problems were symptomatically managed on admission. Grade I and II skin reactions were evident in two patients, one in each grade. The other problems such as fatigue (n= 2, 5.7%), cystitis (n= 2, 5.7%), and Oto toxicity (n=1, 2.9%) were also noticed.

Unplanned admissions

The unplanned admissions to the hospital were observed in 8 patients (22.8%) due to such reasons as bleeding per vagina and pain lower abdomen, cerebrovascular accident (CT scan brain showed metastasis), anemia, shortness of breath, and chest pain (found to have pulmonary embolism). Three patients (8.6%) admitted with chemotherapy-induced toxicity problems.

Gap in chemoradiotherapy

Interruption of the chemoradiotherapy treatment for a period of 1-4 days was observed in 20 patients (57.1%) for the reasons of lack of transportation, unwell, and sick. The split up of twenty patients according to the days of treatment interruption is thirteen patients (37.1%**)** lost one day, 4 patients (11.4%) two days, 2 patients (5.7%) three days, and 1 patient (2.8%) four days.

Discussion

Radical radiotherapy with external radiation plus intracavitary radiation is generally considered as the treatment choice for patients with locally advanced carcinoma of cervix. However, the results can be improved upon. In order to improve the survival rates among the cancer patients, various protocols have been designed, but each protocol has its own limitations. The use of chemoradiotherapy is widely accepted due to the availability of chemotherapy agents and irradiation machines globally (John et al., 1996).

Various theoretical rationales have been provided for chemotherapy before irradiation (Thomas, 2000). It is unclear whether radiation as a radiation sensitizer is beneficial and whether it has any cytotoxic effect at low dosage. Whether the survival rate was improved, and whether increased survival rate was associated with an increase in adverse toxicity remained ambiguous (Symonds, 2002). The use of concomitant chemotherapy is advantageous as it avoids a delay in the implementation of radiation and hence minimal time for overall treatment (Park et al., 2000). Recent studies in cancer of head and neck (Pajak et al., 1991; Stehman et al., 1993) and cervix (Buchler et al., 1993; Lanciano et al., 1993; Perez et al., 1995) indicate that overall treatment duration is important in tumor control. In addition to the above advantages, chemoradiotherapy also inhibits repair of radiation damage and cell synchronization; so that cells move into more sensitive phase of cell cycle, reduction of hypoxic cells, and cytotoxic effect of its own on the cancer cells (Wallner and Li, 1987).

Since both the radiation and chemotherapy have an adverse effect on normal tissue, there is an increased incidence of acute toxicity in the protocol of concomitant chemoradiotherapy. Studies using hydroxyurea, 5-fluorouracil, cisplatin either alone or in combination, demonstrated increasing toxicity

profiles in the combinational therapy (Calkin et al., 1999). Unlike other studies (Bachmeyer et al., 1996; Koren et al., 2002), we did not observe any severe anaphylactic reactions, neurological signs, or ocular complications due to Cisplatin-based chemoradiotherapy.

The hematological toxicities observed in our series were of grade I and II as noted by Singh et al. (2003). We did not notice severe hematological toxicities of grade III and IV as in Shibata et al. (2004) and the meta-analysis of concomitant chemotherapy and radiotherapy for cancer of the uterine cervix by Green et al. (2001). The gastrointestinal toxicities were mainly nausea and vomiting primarily of the grade II and III category, i.e., slightly more than in the Singh et al. (2003). There were no treatment related deaths in our series like in the study by Rose et al. (1999) and Keys et al. (1999). The treatment delay noted in 57.1% of patients due to various reasons mentioned in the results, which is higher than in the Singh et al. (2003). No treatment interruptions in their study related to the treatment toxicities, were noticed in the study.

As reported by Keys et al. (1999), patient compliance in our subjects was good. With the exception of one patient (2 Cycles), all patients received 4-6 cycles of chemotherapy. The present study noted less incidence of severe toxicities related to treatment than reported by Keys et al. (1999). Fifty percent of patients experienced grade I and II toxicity and 22 % required unplanned admission due to tumor and/or treatment related toxicity.

In summary, concurrent chemotherapy with Cisplatin 40mg/m^2 along with radiotherapy is well tolerated; the toxicity was mild and could be manageable easily. Renal parameters in this patient group were normal and there was no evidence of hypomagnesaemia or hypokelemia. Thus, for patients with locally advanced carcinoma of the cervix, concurrent chemoradiotherapy with cisplatin should lead to only mild side effects, but the long-term survival benefits of this combination therapy require further evaluation.

Author contributions

The first author audited all the patients details during his stay at Beatson oncology centre analyzed the data and written the paper. The second and third authors are the consultants in charge of the patients who treated the patients.

Acknowledgements

The author sincerely thanks Dr. M. Ravichandran, Dr. Prasada Rao, Dr. Urban J. D'Souza, and Ms. Kavitha for their encouragement and suggestions in writing the manuscript.

References

1. Advances in the treatment of cervical cancer. International net work for cancer treatment and research, Brussels, Belgium, 20 April 2001 meeting.
2. Al-Tweigeri T, Magliocco AM, and DeCoteau JF. Cortical blindness as a manifestation of hypomagnesemia secondary to Cisplatin therapy: case report and review of literature. *Gynecol Oncol* 72:120-2, 1999.
3. Bachmeyer C, Decroix Y, Medioni J, Dhote R, Benfiguig K, Houillier P, and Grateau G. Hypomagnesemic and hypocalcemic coma, convulsions and ocular motility disorders after chemotherapy with platinum compounds. *Rev Med Interne* 17: 467-9, 1996.
4. Buchler DA, Petereit DG, and Sakaria JN. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 27 (S1):129, 1993.

5. Calkins AR, Harrison CR, Fowler WC Jr, Gallion H, Mangan CE, Husseinzadeh N, Alvarez RD, Mychalczak B, and Podczaski E. Hyperfractionated radiation therapy plus chemotherapy in locally advanced cervical cancer: results of two phase I dose-escalation gynaecologic oncology group trials. *Gynecol Oncol* 75:349 –355, 1999.
6. Cellini N, Morganti AG, Macchia G, Valentini V, Luzi S, and Smaniotti D. Chemoradiation in cervical carcinoma: a must? *Expert Rev Anti cancer Ther* 2:83-89, 2002.
7. Common toxicity criteria of the National Cancer Institute revised and reprinted in 1999.
8. Duenas-Gonzalez A, Cetina L, Mariscal I, and de la Garza J. Modern management of locally advanced cervical carcinoma. *Cancer treat Rev* XX:1-11, 2003.
9. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, and Williams CJ. Survival and recurrence after concomitant chemotherapy and radiotherapy for the uterine cervix: a systemic review and meta-analysis. *Lancet* 358:781-76, 2001.
10. Greentee RT, Hill-Harmon MB, Murray T, and Thun M. Cancer statistics. *CA Cancer J Clin* 51:15-36, 2001.
11. Hershchysyn MM, Aron BS, Boronow RC, Franklin 3rd EW, Shingleton HM, and Blessing JA. Hydroxiurea or placebo combined with radiation to treat stages IIIB and IV cervical cancer confined to the pelvis. *Int J Radiat Oncol Biol Phys* 5:317, 1979.
12. Hornback NB, Shupe RE, Shidnia H, Marshall CU, and Lauer T. Advanced stage III B cancer of the cervix treatment by hyperthermia and radiation. *Gynecol Oncol* 23:160-167, 1986.
13. John M, Flam M, Caplan R, Rotman M, Quivey J, Steinfeld A, and Russell A. Final results of a phase II chemoradiation protocol for locally advanced cervical cancer: RTOG 85-15. *Gynecol Oncol* 61:221–226, 1996.
14. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL, and Gerseu D. A comparision of weekly Cisplatin during radiation therapy versus irradiation alone each followed by adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Eng1 J Med* 340:1154-1161, 1999.
15. Koren C, Yerushalmi R, Katz A, Malik H, Sulkas A, and Fenig E. Hypersensitivity reaction to Cisplatin during chemoradiation therapy for gynecological malignancy. *Am J Clin Oncol* 25: 625-6, 2002.
16. Lajer H and Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev* 25:47-58, 1999.
17. Lanciano RM, Pajak TF, Martz K, and Hanks GE. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-of-care study. *Int J Radiat Oncol Biol Phys* 25:391-397, 1993.
18. Li L, Huang W, and Zhu B. Hypomagnesemia in patients of gynaecologic neoplasms following chemotherapy with Cisplatin. *Zhonghua Fu Chan Ke Za Zhi* 30:363-365, 1995.
19. Lorvidhaya V, Chitapaninarux I, Sangruchi S, Lartsanguasinchai P,Kongthanarat Y, Tangkaratt S, and Visetsiri E. Concurrent mitomycin C, 5-flurouracil and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trail. *Int J Radiat Oncol Biol Phys* 55:1226-1232, 2003.
20. Maor MH, Gillespie BW, Peters LJ, Wambersie A, Griffin TW, Thomas FJ, Cohan L, Conner N, and Gardner P. Neutron therapy in cervical cancer: results of phase III RTOG study. *Int J Radiat Oncol Biol Phys* 14:885-891, 1988.
21. Monk BJ, Tewari K, Burger RA, Johnson MT, Mortz FJ, and Berman ML. A comparison of intracavitary versus interstitial irradiation in the treatment of cervical cancer. *Gynecol Oncol* 67:241-247, 1997.

22. Pajak TF, Laramore GE, Marcial VA, Fazekas JT, Cooper J, Rubin P, Curran WJ Jr, and Davis LW. Elapsed treatment days - a critical item for radiotherapy quality control review in head and neck trials: RTOG report. *Int J Radiat Oncol Biol Phys* 20:13-20, 1991.
23. Park TK, Kim SN, Kim SW, Kim GE, and Suh CO. Concurrent chemotherapy and radiotherapy in invasive cervical cancer patients with high risk factors. *J Korean Med Sci* 15:436-441, 2000.
24. Parkin DM, Bray F, Ferlay J, and Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 94:153-56, 2001.
25. Parkin DM, Pisani P, and Ferlay J. Global cancer Statistics. *CA Cancer J Clin* 49:33-64, 1999.
26. Payrade F, Taillan B, Lebrun C, Bendini JC, Passerron C, and Dujardin P. Hyponatremia during treatment with Cisplatin. *Presse Med* 26:1523-1525, 1997.
27. Perez CA, Grigs PW, Castro Vita H, and Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of treatment and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 32:1275-1288, 1995.
28. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, and Insalaco S. Concurrent cisplatin - based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 340:1144-1153, 1999.
29. Rose PG. Chemoradiotherapy: the new standard care for invasive cervical cancer. *Drugs* 60:1239-44, 2000.
30. Shibata K, Kikkawa F, Suzuki Y, Terauchi M, Kajiyama H, Ino K, and Mizutani S. Usefulness of preoperative chemoradiation in locally advanced cervical carcinoma. *Gynecol Obstet Invest* 57:93-99, 2004.
31. Singh TT, Singh IY, Sharma DT, and Singh NRK. Role of chemoradiation in advanced cervical cancer. *Ind J Cancer* 40:101-107, 2003.
32. Stehman FB, Bundy BN, Thomas G, Keys HM, d'Ablaing G 3rd, Fowler WC Jr, Morter R, and Creasman WT. Hydroxyurea versus misonidazole with radiation therapy in cervical carcinoma: long-term follow-up of a Gynecological Oncology Group trial. *J Clin Oncol* 11:1523-1528, 1993.
33. Stitt JA, Fowler WC Jr, Thomadsen BR, Buchler DA, Paliwal BP, and Kinsella TJ. High dose rate intracavitary Brachytherapy for carcinoma of the cervix: the madixan system. 1. Clinical and radiobiological considerations. *Int J Radiat Biol Phys* 24:383-386, 1992.
34. Strauss HG, Kuhnt T, Laban C, Puschmann D, Pigorsch S, Dunst J, Koelbl H, and Haensgen G. Chemoradiation in cervical cancer with Cisplatin and high dose rate Brachytherapy combined with external beam radiotherapy: results of a phase II study. *Strahlenther Onkol* 178:378-385, 2002.
35. Symonds P. Chemoradiation: the new gold standard for non-surgical treatment of cervical cancer. *Clincal Oncol* 14:201-202, 2002.
36. Thomas GM. Concurrent chemotherapy and radiation for locally advanced cervical cancer: new standard of care. *Sem Oncol* 10:44-50, 2000.
37. United States Deparment of Health & Human Services, NCI clinical announcement. Public health services. NIH: Bethesida, MD, Feb 1999.
38. Wallner KE and Li GC. Effect of cisplatin resistance on cellular radiation response. *Int J Radiat Oncol Biol Phys* 13:587-591, 1987.
39. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, Clarke-Pearson DL, and Liao SY. Randomised comparision of flurouracil plus cisplatin versus hydroxy urea as an adjuvant to radiation therapy in stage IIB-IV A carcinoma of the cervix with negative para aortic lymph nodes: a gynecological oncology group and southwest oncology group study. *J Clin Oncol* 17:1339-48, 1999.