A PHASE I DOSE ESCALATION STUDY OF CISPLATIN CHEMOTHERAPY IN PATIENTS WITH CARCINOMA OF THE CERVIX RECEIVING RADIATION THERAPY

Research Protocol Submitted

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A PHASE I DOSE ESCALATION STUDY OF CISPLATIN CHEMOTHERAPY IN PATIENTS WITH CARCINOMA OF THE CERVIX RECEIVING PELVIC RADIOTHERAPY.

Catherine Naliaka Nyongesa

A dissertation submitted to the Faculty of Medicine in fulfillment of the requirements for a degree of Master of Medicine at the University of the Witwatersrand Johannesburg.

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ABSTRACT

Title

A PHASE I DOSE ESCALATION STUDY OF CISPLATIN CHEMOTHERAPY IN PATIENTS WITH CARCINOMA OF THE CERVIX RECEIVING PELVIC RADIOTHERAPY.

Background

The purpose of this Phase I study was to evaluate the maximum tolerated dose of weekly Cisplatin in a sample population of patients, when given in combination with a radical course of pelvic irradiation.

Patients and Method

Patients, with carcinoma of the cervix stage IB2 through to stage IIIB without hydronephosis, received up to 6 cycles of Cisplatin at weekly intervals. As per standard Phase I methodology, dose escalation occurred after 3 patients had completed at least 6 cycles of chemotherapy at the previous dose level, with DLT (Dose Limiting Toxicity) assessed at each cycle**.** Patients were divided into 3 escalating dose groups of Cisplatin (20, 25, and 30 mg/m^2). Descriptive data analysis was applied, as the primary statistical analysis tool.

Result

Eighteen patients with a median age of 47 years, (range 40 to 68 years) and ECOG performance status 0,1,2 were treated between April 2003 and March 2004 and were evaluated for toxicity and response. All the patients, who received 20 mg/m^2 (n=3) and 25 mg/m^2 (n=3) Cisplatin, had no dose limiting toxicity. Four of the 12 patients, who were given Cisplatin 30mg/m^2 experienced dose-limiting toxicity with a rising creatinine and declining calculated creatinine clearance. The highest serum creatinine was 174 µmol/L. The minimum levels of calculated creatinine clearance were 56, 50.6, 31 and 22 ml/min, respectively.

Conclusion

This study showed that a weekly dose of 25 mg/m^2 of Cisplatin was the maximum tolerated dose when used in combination with pelvic irradiation for this sample of patients. This dose is lower than the recommended dose of Cisplatin 40 mg/m^2/week. The postulated reasons for this result include poor patient nutrition, advanced stage cancer, inherent renal dysfunction in more disadvantaged communities, underlying chronic renal failure, chronic infections, dehydration and volume depletion.

DECLARATION

I, ***Catherine Naliaka Nyongesa***, hereby declare that this report is my own work, except where otherwise acknowledged. It is being submitted in partial fulfillment for the degree Master of Medicine in Radiation Oncology at the University of Witwatersrand, Johannesburg. This thesis has not been submitted before for any degree or examination at this or any other university. The abstract has been accepted for presentation at the following forums:

- For poster presentation at the University of Witwatersrand, Faculty of Health Sciences Research Day on 4th August 2004
- For oral presentation at the Kenya Society of Hematology and Oncology (KESHO) conference Nairobi, Kenya on 22nd August 2004
- For paper/poster presentation at the South African Society of Clinical & Radiation Oncology (SASCRO) & South African Society of Medical Oncology (SASMO) congress 20-23 March 2005 at the Wild Coast Sun, South Africa.

This study has received ethical approval from the University of Witwatersrand's Ethical Committee for Research on Human Subjects. PROTOCOL NUMBER 030212

Signed at: ……..…… on this the …… day of ……. 2005.

Signed: ……

Witness: ……

DEDICATION

I dedicate this work to my parents, Bonaventure and Elemina, and my husband Benedict. Without your love, support, patience and encouragement, I would not have completed my M.MED degree. Thank you.

ACKNOWLEDGEMENT

This study would not have been possible without the help and support of several individuals and I wish to thank them for their assistance in my research.

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6. My daughter, Cynthia Angela, who patiently had to do her homework alone, while I wrote the dissertation.
7. My son, Nelson Khisa, for his patience, although he sometimes got impatient at not being able to sit on mum's lap, while she was writing the dissertation.
8. My sister, Miss Simone Mami J N, who typed the dissertation.

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1.0 INTRODUCTION

Cervical cancer remains one of the most prevalent causes of cancer death in women worldwide. According to Global Cancer Statistics, it is estimated that in the year 2000, the number of patients worldwide, who were diagnosed with cervical cancer was 470,606 and those who died as a result of cervical cancer was 233,372. This was the second most common cancer among women worldwide.[1]

Among the women in sub-Saharan Africa and Latin America, it remains the most common cancer.[1] In South Africa, it is the second most common cancer in the female population and 1 out of 29 women are at risk of developing this cancer at some stage during their lifetime. In 1998 and 1999 it is estimated that between 5,203 and 6,061 new cases were reported each year.[2] It is the most common cancer in Black Females in South Africa with a lifetime risk of LR = 1 : 23.[2] The Department of Radiation Oncology, Johannesburg Hospital, annually treats between 662 and 721 new patients with cervical cancer, as confirmed in personal communications with S. Liebenberg, Cancer Statistics, Johannesburg Hospital Data Base, Department of Radiation Oncology.[3]

In general, very high doses of radiation, which exceed the normal tissue tolerances, are needed to cure locally advanced cancer of the cervix (FIGO stage IIB – IVA). Radiotherapy, when it is the sole treatment, fails to control the progression of locally advanced cervical cancer in 35% to 90% of women.[4]

The rationale for combining chemotherapy with radiation is to eradicate systemic micro-metastases, which are not treated by local radiation. In addition, Cisplatin-based chemotherapy, used in conjunction with radiation, may inhibit the repair of radiation induced sub-lethal damage and by sensitizing hypoxic cells to radiation damage. It may also have an intrinsic cytotoxic effect.[4]

Largely based on the publication of large randomized clinical trials in 1999 and 2000, concomitant chemoradiation using Cisplatin-based regimens is currently the standard treatment for locally advanced cervical cancer.[4, 6,7,8,9.] The treatment of locally advanced cervical cancer is challenging. The five-year survival rates are 80%, 65%, 40%, and <20% for stages IB bulky, IIB, III, and IV, respectively, after treatment with synchronous chemo-radiotherapy.[11] It is hoped that molecular targeted therapy may render the treatment of this cancer more successful.

Cisplatin pharmacology

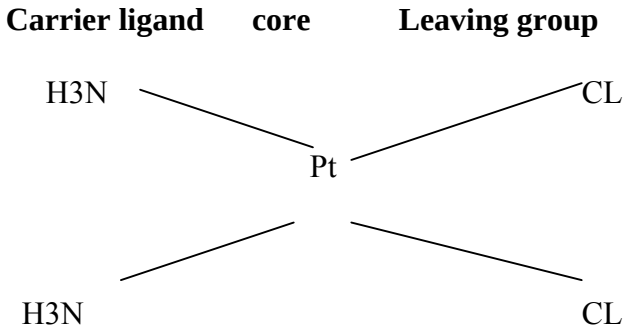
Platinum compounds are widely used in the treatment of solid tumours. Rosenberg discovered Cisplatin serendipitously, while investigating the effects of electric currents on bacteria in 1965.[12] Wiltshaw did the first clinical studies on Cisplatin in the early 1970s.[13,14]

Cisplatin [Cis-diamminedichloroplatinum II (CDDP), Figure 1] exerts anti-tumour activity similar to classical alkylating agents.

The drug becomes aquated in the tissues and can then interact with macromolecules, such as DNA, to form intrastrand adducts and interstrand cross-links.[15, 16] The aquated platinum species binds preferentially with highly nucleophilic N-7 positions of the purine bases guanine and adenine.[15] The intrastrand adducts account for well over 90% of total platinum binding to DNA.[18, 19] Cisplatin can also bind to RNA and cellular proteins.[20] The major effect of Cisplatin is to inhibit cell replication and DNA synthesis.[17]

FIGURE 1

Structure of Cisplatin[15, 16]



Cis-diamminedichloroplatinum (II)

Following intravenous (IV) administration, Cisplatin is bound to plasma proteins. Approximately a quarter of the intravenous dose is excreted through the kidneys during the first 24 hours. The total Cisplatin (free and bound) has a prolonged half-life of 2 to 3 days. Cisplatin can remain bound to protein tissues for a long period of time.[15]

Cisplatin potentiates the sublethal damage induced by radiation[21] and inhibits repair of potentially lethal damage.[22] Cisplatin radiosensitization is a free radical mediated by its ability to scavenge for free electrons formed by the interaction between radiation and DNA. The reduction of the platinum moiety may serve to stabilize DNA damage that would otherwise be irreparable. The additive effects of Cisplatin are improved when the drug is administered with fractionated radiotherapy. This is explained by its inhibition of sub-lethal damage repair.

Toxicity from Cisplatin

The most common and most feared side effect of Cisplatin in patients, who do not receive adequate premedication, is emesis. Nausea and vomiting can be acute or delayed (≤ 24 or > 24 hours post chemotherapy, respectively). This side effect has been alleviated by the introduction into routine clinical practice of 5-hydroxytryptamine-3 ($5HT_3$) receptor antagonists, for example, Granisetron or Ondansetron, which have significantly reduced the incidence of acute Cisplatin-induced emesis.[24] Prophylaxis against delayed emesis is recommended. In addition to 5-HT3 receptor antagonists, corticosteroids are required to help control nausea and vomiting.[25,26,27,28.)]

Cisplatin-induced nephrotoxicity was dose limiting in early clinical trials.[16] Nephrotoxicity can be minimized by hydration with normal or hypertonic saline and by maintaining good diuresis with mannitol or frusemide, if necessary.[29,30, 31,32,33.)] Dose adjustments must be made based on the glomerular filtration rate (GFR). If this is more than 50 ml/min, full doses may be given, but if it is less than 30 ml/min, Cisplatin should not be administered. For a GFR

between 30 ml/min and 50 ml/min, the Cisplatin dose must be reduced in proportion to the GFR.[16] Reed recommended that alternative chemo-therapeutic agents should be considered, if the 24 hour creatinine clearance is < 60 ml/min.[15]

A loss of cations in the urine is common after treatment with Cisplatin.[15] In particular, hypomagnesaemia occurs, despite adding magnesium to the hydration fluid. Hypocalcaemia and hypokalaemia are common.

Neurotoxicity is currently the main dose-limiting toxicity of Cisplatin.[16] This can manifest as peripheral neuropathy and ototoxicity. Ototoxicity consists of tinnitus or high frequency hearing loss. Furosemide is ototoxic and, if it is used with Cisplatin, it could theoretically potentiate the Cisplatin induced ototoxicity. Severe ototoxicity may result from high doses of Cisplatin.[35] Lhermitte's sign, autonomic neuropathy seizures and encephalopathies are less common. Neurotoxicity is dose-dependent and is generally found in patients, who receive a total dose of more than 300 mg/m^2.[34] Neurotoxicity can, however, be seen after only one dose of Cisplatin. Most neurotoxic side effects will disappear after withdrawal of the drug.

Cisplatin-induced myelosuppression is mild, but reversible. Dose related anaemia, leucopaenia, and thrombocytopaenia are found. Severe thrombocytopaenia or leucopaenia occurs in 5% of cases.[35] Hypersensitivity reactions are rare.

TABLE 1.0

Trials of concurrent chemotherapy with radiation in cancer of the cervix

Trial	n	Stage	Treatment	Overall survival (3-year) %
Whitney et al GOG 85[8]	368	IIB – IVA	CDDP + 5FU H U	67 57
Rose et al GOG 120[4]	526	IIB – IVA	CDDP CDDP+5FU+HU H U	65 65 47
Keys et al GOG 123[7]	369	Stage IB (Bulky)	CDDP -	83 74
Morris et al RTOG 9001[6]	403	IIB – IVA	CDDP + 5FU -	75 63
Peters et al SWOG 8797[9]	243	IA_2 – IIA	CDDP + 5FU -	87 77

CDDP= Cisplatin, 5-FU= 5-Fluorouracil, HU = Hydroxyurea.

n = number of patients

What is a phase I study? (Figure 2)

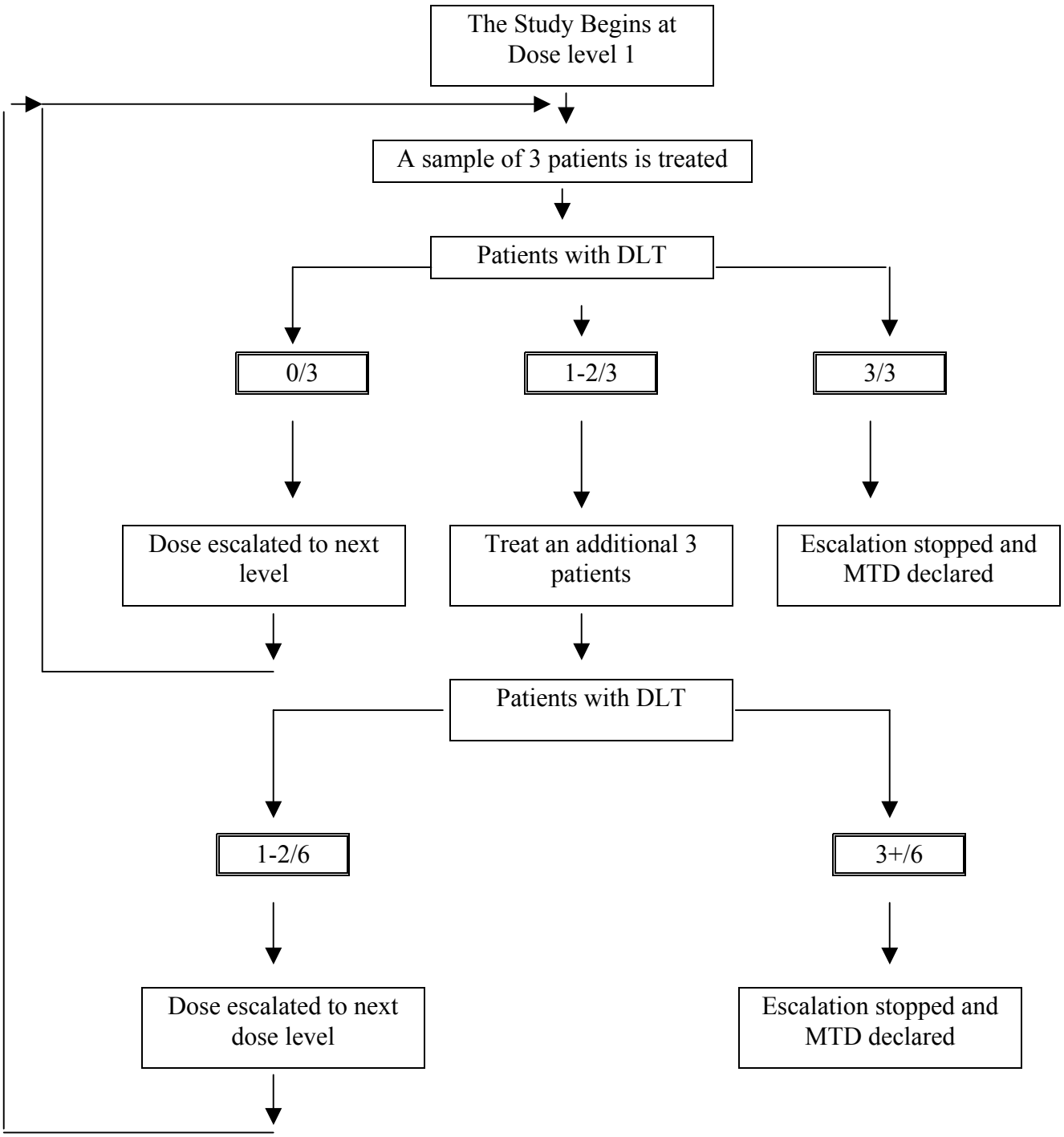
The basic design is that of dose escalation in small patient samples until such time as treatment toxicity reaches a predetermined level, or unexpected toxicity is seen.[38] Thus, stepwise testing in phase I trials determines the maximum tolerated dose (MTD). A dose limiting

toxicity (DLT) is normally grade III-IV toxicity. The key parameters that should be defined at the outset of a phase I trial include patient eligibility criteria, starting dose, the schedule of dose escalation, the sample size of each dose level and the expected or estimated MTD.[39]

The primary objective of phase I trials is to evaluate toxicity and to establish a recommended drug dose for a given administration schedule. An additional objective is to investigate the drug's anti-tumour activity and objective tumour responses to new drugs. This offers assistance in determining specific tumour types for subsequent phase II trials. Patients with various tumours are, accordingly, usually registered in phase I trials.[37] In cases where certain information on the anti-tumour activity of a drug is available (as in this study), patients can be specifically selected so as to maximize the potential response.

FIGURE 2

Standard design of phase I studies in oncology.[40]



2.0 LITERATURE REVIEW

The majority of the clinical trials of concurrent chemotherapy and radiation therapy strategies for the treatment of cervical cancer have been conducted on patients with locally advanced disease.

1st Generation Trials

Piver et al 1983[45]

In a randomised controlled trial of 40 patients with stage IIB cervical carcinoma treated at Roswell Park Memorial Institute with radiation therapy and hydroxyurea versus placebo, Piver reported a significant survival advantage in the hydroxyurea arm. All the patients underwent pre-treatment surgical staging, which documented the absence of paraaortic lymph node metastasis. The 5-year survival was 94% in the hydroxyurea group, versus 53% in the placebo group.

Hreshchyshyn et al 1979, (GOG 4)[46]

Hreshchyshyn conducted a trial of hydroxyurea, versus placebo with concomitant radiation therapy in patients with stage IIIB – IV cervical cancer. Several problems were identified in the conduct of this study, including the lack of either radiological imaging or retroperitoneal surgical staging of the aortic lymph nodes. Among the 190 women treated in this trial, only 104 were evaluable for toxicity and only 97 were evaluable for survival. Consistent with Piver's experience, the frequency of leucopaenia in the hydroxyurea treated group was substantial. Complete tumour regression was reported for 68% in the hydroxyurea group,

versus 49% in the placebo group. The expected median survival was also improved with the administration of hydroxyurea (19.5 months versus 10.7 months).

2nd Generation Chemoradiation Trials

This generation of clinical trials of chemoradiation for locally advanced cervical carcinoma tested compounds with high electron affinity, which mimick the effects of oxygen as closely as possible, namely, "hypoxic cell sensitizers". The nitroimidazoles were the most widely researched of these compounds and misonidazole was the first of the nitroimidazoles to be combined with radiation therapy for the treatment of cervical cancer.

Stehman et al 1993[47,48]

A Gynae Oncology Group (GOG) reported on a Phase III trial of misonidazole versus hydroxyurea in combination with radiation therapy in patients with stage IIB – IVA cervical cancer. The initial publication of the clinical trial results did not report a survival difference between the 2 arms. The pelvic failure rate was higher in the misonidazole group (23.6%), than in the hydroxyurea group (18.0%), and the overall recurrence rate was also higher in the misonidazole group, (44%) versus the hydroxyurea group (37%). After extended follow-up, a subsequent analysis confirmed both progression-free and overall survival advantages for the hydroxyurea group.

3rd Generation Chemoradiation Trials in the United States

These trials used Cisplatin based chemotherapy.

Whitney et al 1999, (GOG 85)[8]

Whitney published the results from an inter-group study conducted by the GOG and the South West Oncology Group (SWOG). This study compared concurrent Cisplatin plus 5-FU chemotherapy and pelvic radiation therapy, with Hydroxyurea plus pelvic radiation therapy. All the patients treated had stage IIB – IVA disease and negative common iliac and aortic lymph nodes, as was confirmed by pre-treatment surgical staging. There were 386 eligible patients and the median follow-up time among surviving patients was 8.7 years. Disease progression occurred in 43% of the patients, who received Cisplatin plus 5-FU, versus 53% of patients, who received Hydroxyurea. The progression free survival was significantly better among patients treated with Cisplatin plus 5-FU ($p = 0.033$). The 3-year survival rate for women, who received Cisplatin plus 5-FU, was 67%, versus 57% for women, who received Hydroxyurea.

Ninety one percent of patients, who were randomised to Cisplatin plus 5-FU, received both drugs and 10% received fewer than 4 courses. The side effects were predominantly gastrointestinal and haematologic in both treatment arms. More grade III-IV leucocytopaenia was found in the Hydroxyurea arm than in the Cisplatin plus 5-FU arm, 4% and 24% respectively. Gastrointestinal side effects were more pronounced in the Cisplatin + 5-FU group (8%) than in the Hydroxyurea arm (4%) (Table 2.0).

Morris et al 1999 (RTOG 90 - 01)[6]

Morris treated 403 patients with concurrent Cisplatin plus 5-FU chemotherapy plus pelvic radiation therapy versus extended field radiation therapy. The eligibility requirements for this trial differed from the previous GOG studies in that it included patients with stage IB2 – IIA cervical cancer. With a median follow-up of 43 months, the estimated cumulative 5-year survival rates were 73%, versus 58%, respectively, for patients treated with chemo-radiation therapy versus radiation therapy alone ($p = 0.004$). A significant difference in disease-free survival was noted in the chemotherapy group. The addition of chemotherapy to radiation therapy was effective in reducing the frequency of both local recurrences and distant metastasis ($p < 0.001$). More grades 3-4 acute side effects were found in the chemo-radiotherapy group, as illustrated in Table 2.1. There were no significant differences in late complications in the two treatment groups.

Eifel et al 2004 (RTOG 90 - 01 update)[49]

Eifel reported on the mature results of the Morris et al trial, as described above, which compared pelvic plus para-aortic radiation (extended field radiotherapy), versus pelvic radiotherapy with concurrent Cisplatin and 5-FU. The medium follow up time was 6.6 years for the 228 surviving patients. The addition of Cisplatin and 5-FU to radiotherapy led to a significant improvement in the survival rate of patients with locally advanced cancer of the cervix, without increasing the rate of treatment-related toxicity. The overall survival rates at 8 years (67% versus 41%, $p<0.0001$) was much improved in the combined modality arm. This approach of concurrent chemo-radiotherapy is preferred over the use of para-aortic radiation alone in a prophylactic setting.

Rose et al 1999 (GOG 120)[4]

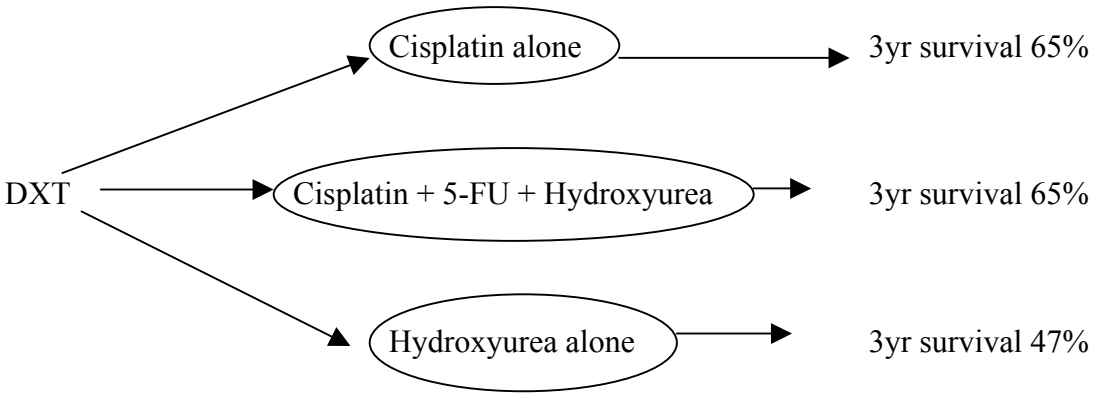
Rose enrolled 526 patients in a 3- arm trial of pelvic radiation therapy plus concurrent, single-agent Cisplatin, versus Cisplatin plus 5-FU plus Hydroxyurea, versus Hydroxyurea alone (Figure 3 below). All patients had stage IIB – IVA cervical cancer with surgically confirmed negative common iliac and aortic lymph nodes. The median duration of follow-up was 35 months. Both groups of patients, who had received Cisplatin, had longer progression-free survivals than the patients who had received Hydroxyurea alone ($p<0.001$). The addition of 5-FU did not increase the response rate, or the survival, but did increase the toxicity. The authors recommended weekly doses of Cisplatin, as the standard drug for chemo-radiation therapy of cervical cancer.

The median time of treatment duration was 9 weeks for the group receiving weekly Cisplatin with radiotherapy, with a median delay of 8 days in administering radiotherapy. Table 2.2 illustrates the number of chemotherapy cycles received in the Cisplatin arm. Only half of the patients received at least 6 cycles of Cisplatin chemotherapy.

The eligibility criteria for the clinical trial mandated a serum creatinine level of not more than 2.0 mg/dL (177 μmol/L) per patient. Cisplatin was discontinued, if the serum creatinine rose to more than 2.0 mg/dL. The Cisplatin dose was reduced to $30mg/m^2$/week for grade 2 neurotoxicity and grade 4 emesis and it was discontinued for grade 3 or higher neurotoxicity. The group receiving 3 drugs had more grade 3 - 4 haematologic toxicity than the other two arms. The types of adverse events for radiotherapy and Cisplatin are shown in Table 2.3.

FIGURE 3

GOG 120 Study[5]



Peters et al 2000 (SWOG 8797)[9]

Peters reported the results from an inter-group trial conducted by SWOG and GOG. 268 patients with cervical cancer stage IA2 – IIA were randomized, of which 243 patients were assessable. All the patients participating in the trial had undergone a radical hysterectomy and lymph node dissection and had positive pelvic lymph nodes, positive surgical margins or tumour extension to the parametria. Eligible patients were randomized to receive either chemoradiation with Cisplatin plus 5-FU, or radiation therapy alone. The addition of Cisplatin plus 5-FU chemotherapy to radiation therapy improved both the progression-free and overall survivals. The median follow-up was 43 months. The projected 4-year survival rate for women on the concurrent Cisplatin and 5-FU and irradiation arm was 81%, versus 71% for women in the pelvic radiation arm. The difference was statistically significant. Only 71% of the patients in the chemo-radiotherapy arm received at least three cycles of chemotherapy. The GIT and haematologic toxicity was greater in the women who were in the chemo-radiotherapy group as depicted in Table 2.4.

Keys et al 1999 (GOG 123)[7]

Keys treated 369 patients, with bulky stage IB2 cervical cancer, with weekly Cisplatin plus radiation therapy versus radiation therapy alone. All patients had a CT Scan, lymphangiography, or negative aortic lymph nodes as was confirmed by pre-treatment surgical staging. An extrafascial hysterectomy was performed 3 to 6 weeks after the conclusion of the radiation-based treatment. The progression-free and overall survivals were significantly higher among the patients, who had received concurrent Cisplatin. The 3-year survival rates were 83% for the chemotherapy group, versus 74% in the arm, who had received radiation alone ($p = 0.008$).

90% of the patients in the chemoradiotherapy arm received at least 4 cycles of chemotherapy. There were no treatment delays due to chemotherapy, as the median duration of the radiotherapy was 50 days in both arms. There were more grade 3 or 4 adverse events in the combined arm compared to radiotherapy alone, namely, 35% versus 13%, respectively. The majority of these toxic effects were haematologic and gastrointestinal. (See Table 2.5)

The results from the 5 American clinical trials referred to above, [4, 6,7,8,9.] demonstrate that Cisplatin based chemotherapy, when given concurrently with radiation therapy, prolongs survival in women with stage I – IIA disease, who have:

- metastatic disease in the pelvic lymph nodes;
- parametrial disease;
- or positive surgical margins at the time of primary surgery; and
- locally advanced cervical cancers.

Based on these trials, Cisplatin-based concurrent chemoradiation is the recommended standard of care for patients with bulky FIGO stage IB through to stage IVA cervical cancer.

These trials were distinguishable in that different stages of disease were treated, different doses of radiation were used and the scheduling of Cisplatin and 5-Fluorouracil (5-FU) varied. Only two of the five trials used weekly doses of Cisplatin, namely, GOG 120 and GOG 123. The dose of Cisplatin used in these two trials was 40 mg/m^2 intravenous weekly, with a maximum weekly dose of 70 mg/m^2.[4, 7]

The GOG 120 study was a landmark trial in that it established Cisplatin as the single agent of choice for chemoradiation of locally advanced cervical cancer.

These results had a significant impact on the standard of care for treatment of cervical cancer. As a result of the GOG 120 trial, the National Cancer Institute, in 1999, issued a clinical announcement to the effect that "*Strong consideration should be given to the incorporation of*

concurrent Cisplatin based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer".[73] Two common difficulties with this treatment protocol are acute toxicities and completion of the prescribed chemotherapy regimen.

Duenas et al 2003[42]

Duenas presented results from a recent meta-analysis comparing the most common treatment modalities versus radiation therapy alone, in patients with locally advanced cancer of the cervix. The results are illustrated in Table 2.6.

3rd Generation Randomised Chemoradiation Trials in Other Countries

Wong et al 1999 (Chinese study)[48]

Wong treated 220 patients with clinically staged bulky stage II - III cervical cancer with either standard pelvic irradiation alone, or combined with Epirubicin (Epirubicin 60 mg/m^2 at start + Epirubicin 90 mg/m^2 every week for 5 courses). The median follow-up was 77 months. Patients who received irradiation and Epirubicin had a significantly longer disease-free and cumulative survival rate than those, who were treated with radiation therapy alone. The 9-year cumulative survival was 78% in the chemo-radiation arm, versus 66% in the radiation arm.

Roberts et al 2000 (Venezuela/Yale University)[49]

Roberts reported on 160 patients with stage IB - IVA disease randomized to receive either irradiation alone, or chemoradiation. Concurrent chemotherapy consisted of Mitomycin C 15 mg/m^2 in weeks 1 and 6. There was a significant improvement in the disease-free survival of

all patients in the chemotherapy arm. The disease free survival at 4 years was 82% (p = 0.03) in the chemoradiation arm, versus 75% in the radiation arm.

Negative Trial

Pearcey et al 2002 (Canadian Trial)[5]

Two- hundred and fifty nine patients participated in this National Cancer Institute (NCI) of Canada study. Patients with FIGO Stage IB – IVA cervical cancer having central disease of more than 5 cm, with positive histologically confirmed pelvic lymph node involvement, were randomized. 127 patients received radiotherapy with concurrent Cisplatin chemotherapy 40 mg/m^2 weekly X 6 (arm 1), and 126 patients received radiotherapy only (arm 2). At a median follow up of 82 months there were no significant differences between the two arms in the 3 and 5-year survival rates (3-year – 69% arm 1 versus 66% arm 2 and 5-year – 62% arm 1 versus 58% arm 2: p = 0.42). This study did not show a benefit for either pelvic control or survival by adding concurrent weekly Cisplatin chemotherapy in a dose of 40 mg/m^2 to radical radiotherapy.

These results, which conflict with the results of previous clinical trials, could have been caused by a higher incidence of anaemia in the Cisplatin receiving arm, which may have had a negative influence on the efficacy of radiotherapy in this arm. It was postulated that the Cisplatin chemotherapy is effective, if the radiotherapy is protracted as in the GOG 120 and GOG 85.[4, 8] In those trials, there was a delay in delivery of radiation with the median treatment duration being 62 and 64 days, respectively, compared to the duration of 51 days in the Canadian trial. It is generally accepted that there is a 1.2% loss of local control for each

day the treatment is protracted and this may have exaggerated the benefit of adjuvant chemotherapy in the GOG trials.

Trials reporting on toxicity of concomitant chemoradiotherapy

Kantardzic et al 2004[50]

80 patients were randomized into 2 arms. The 1st arm of 40 patients received chemoradiotherapy and the 2nd arm of 40 patients received radiotherapy alone. All the toxicities were reported using the CTC criteria. After three months of follow up, there was no difference in acute toxicity between the two arms.

Tan et al 2004[51]

74 patients received radical radiotherapy given concurrently with chemotherapy. The toxicity was recorded using the CTC criteria. The most common side effects were diarrhea (80.6%), malaise (66.7%) and nausea (62.5%). Only 3 patients had grade 3 - 4 toxicity (1 patient grade 3 thrombocytopaenia, 1 patient grade 4 neutropaenia and the 3rd patient had grade 3 diarrhoea). Haematological toxicity was mainly anaemia with 41.7% of the patients developing grades 1-2 toxicity. Only 70.2% of the patients completed the planned number of chemotherapy cycles, with a further 20.3% receiving at least 3 cycles. Most patients failed to complete the planned chemotherapy due to gastrointestinal toxicity.

Serkies et al 2004[52]

112 patients, with a median age of 48 years, were treated with radiotherapy plus weekly Cisplatin at 40 mg/m^2. Overall 74% of the patients received at least 4 Cisplatin cycles. The

planned five Cisplatin cycles were given to only 45% of the patients. A full and timely Cisplatin dose was administered to 26% of the patients. The most common toxicities reported were gastrointestinal and renal in nature.

Cisplatin Dose Studies

Twiggs et al 1986[53]

Twiggs reported on a dose escalating toxicity study using concurrent weekly Cisplatin and radiotherapy in patients with advanced cervical cancer**.** A total of 16 patients with cancer of the cervix FIGO stage IB – IVB participated. Patients were treated with two dose levels, namely, Cisplatin 10 mg/m^2/week and 20 mg/m^2/week. There was no escalation beyond Cisplatin 20 mg/m^2/week, as previous experience indicated that higher doses resulted in unacceptable toxicity in head and neck cancer patients**.** A total of 4 patients were treated with Cisplatin 10 mg/m^2/week and 12 patients were treated with Cisplatin 20 mg/m^2/week. The percentage of prescribed Cisplatin cycles administered were 87% and 79%, respectively, at these dose levels. Doses of Cisplatin 20 mg/m^2/week were well tolerated with no life threatening toxicity and patient compliance was good.

Souhami et al 1993[54]

This was a prospective single arm phase I/II trial. 50 patients were treated with Cisplatin 30 mg/m^2/week starting on the first day of radiotherapy. This dose was chosen based on a dose finding study performed by Schaake-Koning,[55] in lung cancer patients. The Cisplatin was administered over a period of 1 hour in 250 ml of NS, or 3 % NaCl following prehydration with at least a ½ litre of fluid over a period of 1 to 1 ½ hours. The median number of cycles

administered was 5 and a total of 82% of the patients received 4 or more cycles. No renal abnormalities were reported. The acute toxicity is detailed in Table 2.7.

A high response rate was noted with this regimen, but the regimen was also associated with a relatively high frequency of late GIT complications.

Malfetano et al 1993[56]

Malfetano conducted a phase I – II trial of weekly Cisplatin with radical radiotherapy in patients with FIGO stage IIB – IVB, recurrent and poor prognostic cervical carcinoma. The weekly Cisplatin dose was 1 mg/kg (not to exceed 60 mg/week). This regimen was well tolerated with no interruption in the administration of radiotherapy. Cisplatin was not administered, if the serum creatinine was more than 2.0 mg/dL. Only 64% of the patients completed at least 5 cycles of chemotherapy without interruption (Table 2.8). There was little or no nausea and the nausea was confined to the day of the Cisplatin administration. There was no nephrotoxicity and other side effects were minimal.

TABLE 2.0

Side effects in the RT with 5-FU+CDDP group (n=169)- Whitney et al [8]

Side effect	% of patients				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leucocytopaenia	55.0	23.1	18.3	2.4	1.2
Thrombocytopaenia	96.4	2.4	1.2	0.0	0.0
Other haematologic	73.4	14.2	9.5	2.4	0.6
GIT	31.4	22.5	38.5	5.3	2.4
Genitourinary	74.0	17.8	7.1	1.2	0.0
Neurologic	95.9	3.0	1.2	0.0	0.0
Cutaneous	77.5	14.8	5.3	2.4	0.0
Fever	95.9	1.8	1.2	1.2	0.0

TABLE 2.1

Worst acute toxicity (grade 3 - 4) Morris et al [6]

Toxicity	Chemo RT n=195		RT alone n=193	
	Grade 3	Grade 4	Grade 3	Grade 4
Cutaneous	4	1	0	1
N/V	14	3	2	0
Bowel/rectal	12	5	1	0
Bladder	2	0	0	0
Haematologic	57	16	2	0

TABLE 2.2

Number of chemotherapy cycles received in the Cisplatin group - Rose et al [4]

Chemotherapy Cycles	Number of Patients (%)
≥ 6	89 (49.4)
5	59 (33.5)
4	18 (10.2)
3	7 (4.6)
2	2 (1.1)
1	2 (1.1)
0	1 (0.6)

TABLE 2.3

Toxicity in the Cisplatin arm - Rose et al [4]

Toxicity	**Cisplatin 40 mg/m^2/week with pelvic irradiation**				
	n = 176				
	Grade	**Grade**	**Grade**	**Grade**	
Grade					
	0	1	2	3	4
Leucocytopaenia	34	17	26	21	2
Thrombocytopaenia	79	15	4	2	0
GIT	77	11	6	3	2
Neurologic	85	6	8	1	0
Febrile Neutropaenia	94	2	4	0	0
Hypomagnesaemia	92	3	2	2	2
Other	90	5	2	1	2

[1]Other: Rising serum creatinine to more than 3 to 6 times the normal upper limit, electrolyte abnormalities, dehydration and liver infections.

TABLE 2.4

Major toxicity – Peters et al [9]

Toxicity	**Chemo RT n=122 No. patients with toxicity**		**RT alone n=112 No. patients with toxicity**	
	grade 3	**grade 4**	**grade 3**	**grade 4**
Anaemia	3	1	0	0
Diarrhoea	8	4	6	1
Leucocytopaenia	40	3	1	0
Nausea	17	0	1	0
Renal failure	0	0	0	0
Thrombocytopaenia	1	0	0	0
Vomiting	12	3	0	0

TABLE 2.5

RT with weekly Cisplatin 40 mg/m^2 (n = 183) – Keys et al[7]

Toxicity	**% of patients with toxicity**				
	grade 0	**grade** 1	**grade** 2	**grade** 3	**grade** 4
Haematological	23	20	36	18	3
GIT	28	31	27	9	5
Genitourinary	67	23	8	0.5	1
Cutaneous	86	10	4	0	0
Neurological	91	3	5	1	0
Other	75	13	5	5	2

TABLE 2.6

Results of 3 Meta-analysis[42]

Control arm	Experimental arm	Results
Radiation therapy only	RT after neoadjuvant chemotherapy	No survival advantage
Radiation therapy only	Surgery after neoadjuvant chemotherapy	5 year survival increased by 15%
Radiation therapy only	Cisplatin based concurrent chemoradiotherapy	5 year survival increased by 12%

TABLE 2.7

Acute toxicity - Souhami et al [54]

Toxicity	Grade I (%)	Grade 2 (%)	Grade 3 (%)
Nausea /vomiting	3(6)	25(50)	1(2)
GIT	4(%)	12(24)	1(2)
Genitourinary	1 (%)	5(10)	-
Haematologic	-	1(2)	1(2)
Skin	-	-	2(4)

Note: patients could have more than one complication.

TABLE 2.8

Cisplatin cycles delivered in Malfetano study[56]

Number of cycles	Number of Patients (%)
6	17 (31%)
5	28 (51%)
4	9 (16%)
3	1 (2%)

TABLE 2.9

Acute toxicity in group II- Wong et al[61]

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	15	3	2	2	0
Leucocytopaenia	15	2	1	4	0
Thrombocytopaenia	17	2	3	0	0
Nausea & vomiting	0	17	5	0	0
Diarrhoea	14	5	3	0	0
Alopecia	0	0	14	8	0

Bonomi et al 1982[57]

The GOG group conducted a prospective study involving 381 patients with cervical cancer, who were selected to receive three different dose regimens:

(a) high dose Cisplatin 100 mg/m^2 or (b) Cisplatin 20 mg/m^2 daily for 5 days and (c) low dose Cisplatin 50 mg/m^2.

Each of these regimens was repeated every 21 days. (Maximum total Cisplatin dose was 400 mg/m^2). There was no difference in survival or response between the three regimens, but there was increased toxicity in the high dose arm. The responses were 27%, 24% and 23% respectively, while the median survival was 7.0, 6.1 and 6.8 months, respectively.

Piver et al at Roswell Park 1983[58]

In a previous study by Wiltshaw, the use of high dose Cisplatin in ovarian cancer resulted in severe nausea and vomiting.[59] Another study utilizing lower doses of Cisplatin at 1 mg/kg weekly in ovarian carcinoma showed a high degree of activity.[60] Based on these trials, Piver conducted a phase III trial comparing low dose versus high dose Cisplatin 1 mg/kg weekly for 6 weeks, versus high dose Cisplatin 100 mg/m^2 every 4 weeks in patients with recurrent carcinoma of the cervix. 18 patients received the weekly Cisplatin and 14 received the high doses of Cisplatin. There was severe nausea and vomiting in the high dose arm, which symptoms persisted for up to one week after completing chemotherapy. This led to the modification of the treatment protocol and Cisplatin 100 mg/m^2 was then administered over 5 days. With this regimen, there was moderate nausea and vomiting, which subsided within 48 hours after completion of the chemotherapy. Conversely, the low dose group of Cisplatin, at 1 mg/kg weekly, suffered from moderate nausea and vomiting, which subsided within 24 hours after completion of the treatment. The most tolerable regimen in this study was the weekly, low dose Cisplatin.

Wong et al 1989[61]

Wong conducted a three-arm trial with 64 patients in the following manner:

- Arm I - radiotherapy only - 25 patients
- Arm II - radiotherapy with concomitant weekly Cisplatin 25 mg/m^2 - 22 patients
- Arm III – radiotherapy with concomitant twice weekly Cisplatin – 25 mg/m^2 - 17 patients

Cisplatin was discontinued if the creatinine clearance dropped below 50 ml/min. It is not reported, however, if there were any patients, whose creatinine clearance levels actually dropped. There was a better initial response in arm III patients, but the overall survival was the same in all three arms. The acute toxicity in arm II is detailed in Table 2.9. In summary, there is little evidence relating to the weekly use of Cisplatin 40mg/m^2 in the treatment of carcinoma of the cervix. For this reason this dose escalation study has been undertaken to establish the required dose of Cisplatin.

Chemotherapy and Hyperfractionated Irradiation

Calkins et al 1999 (GOG 8801 & 8901)[62]

Calkins assessed the toxicity of hyperfractionated whole pelvis radiotherapy (1.2 Gy twice daily) plus concurrent chemotherapy for locally advanced cancer of the cervix. In the first GOG study (8801) 38 patients were treated with Hydroxyurea before radiation. In the second study (GOG 8901), 30 patients were treated with Cisplatin plus 5-FU before radiation. There was no obvious correlation between pelvic failure rates and the radiation dose or the chemotherapy regimens used. The MTD of pelvic radiation was 57.6 Gy in 48 fractions.

Thomas et al 1998[63]

Thomas conducted a 4- arm study on 234 women with cervical cancer stage IB (bulky) to IVA. These patients received either standard external beam radiation, with or without 5-FU chemotherapy, versus hyperfractionated radiation therapy, with or without 5-FU chemotherapy. A subset analysis demonstrated a significantly better 5-year disease-free survival rate for those patients with stage IB, IIA or IIB (early medial parametrial disease) receiving concurrent standard radiation therapy and 5-FU compared to the hyperfractionated arms.

Neoadjuvant Chemotherapy Trials

The studies of **Kumar et al 1998,**[64] **Leborgne et al 1997,**[65] **Sundfør et al 1996,**[66] **Herod et al 2000**[67] and **Symonds et al 2000**[68] failed to demonstrate any significant role of neoadjuvant chemotherapy before standard radiation therapy.

3.0 CISPLATIN PHASE I TRIAL

Background

In the radiation oncology unit of Johannesburg Hospital, concomitant Cisplatin given with radiation is the standard treatment for patients undergoing radical radiotherapy for carcinoma of the cervix. Initially, a weekly dose of 30 mg/m^2 of Cisplatin from week 1 to 6 of radiation therapy was administered. On escalation of the dose to 35 mg/m^2, it was noted that some patients developed leucopaenia and were unable to continue with the weekly Cisplatin. It was

suspected that these patients might have a decreased tolerance to weekly doses of Cisplatin above 30 mg/m^2. It was postulated that this decreased tolerance could be related to socioeconomic or nutritional factors.

STUDY OBJECTIVES

1. To find the maximum tolerable weekly dose of Cisplatin tailored to the sample of patients.
2. To escalate the dose of Cisplatin from 20 mg/m^2, by 5 mg/m^2 increments, for subsequent patients, depending on tolerability.
3. To evaluate the dose limiting toxicity (DLT) of Cisplatin, when used in combination with radical radiotherapy. To evaluate the haematological, gastrointestinal, neurological and renal side effects.

Eligibility Criteria

This was a phase I study conducted at the University of Witwatersrand Departments of Medical Oncology and Radiation Oncology Johannesburg Hospital, Johannesburg, South Africa. The local Human Research Ethics Committee approved this study. To be eligible to participate in this phase I study, patients had to comply with the following criteria:

a) Biopsy proven untreated invasive carcinoma of the cervix.
b) FIGO stage IB2 through to IIIB without hydronephrosis undergoing radical radiotherapy.
c) ECOG status 0 – 2.
d) Over 18 years of age.

e) Adequate renal function (calculated creatinine clearance of ≥ 60 ml/min according to the Cockroft and Gault formula).

f) HIV negative.

g) Reliability as regards follow-up procedures.

h) Hb ≥ 10 g/dl, WBC ≥ 3.0 x 10^9/L, platelets ≥ 100 and absolute neutrophil count ≥ 1.8 x 10^9/L.

i) Signed consent form as approved by the Ethical Committee for Research on Human Subjects, confirming patient awareness of the investigational nature of the study.

Exclusion criteria

The following criteria excluded patients from participation in this phase I study:

1. Prior invasive cancer.
2. Medical contraindications to chemotherapy.
3. Prior pelvic irradiation.
4. Prior systemic chemotherapy.

Treatment plan

All patients underwent staging using FIGO (International Federation of Gynecology and Obstetrics) criteria. A chest radiograph and abdominopelvic sonar were performed routinely. Intravenous pyelogram, lymphangiogram, cystoscopy and sigmoidoscopy were not performed, unless clinically indicated. Pre-treatment surgical staging was not required.

Radiotherapy

External beam mega-voltage RT was administered to a clinical target volume that included the primary cancer, uterus, internal iliac, presacral, upper external iliac and lower common iliac lymph nodes. Patients with stages IB2, IIA and IIB lesions received 46 Gy external beam therapy delivered homogeneously to the pelvis 5 days/ week in 23 fractions at 2 Gy per fraction. This was supplemented with high dose rate brachytherapy 6.5 Gy x 4 fractions.[69]

Patients with stage IIB distal (outer half of parametria involved), IIIA and IIIB early (fixed to one pelvic sidewall only) received 50 Gy in 25 fractions at 2 Gy per fraction 5 days per week + HDR brachytherapy 8 Gy x 3 fractions.

An AP – PA or "*four field box technique*" was used depending on the AP separation and weight of the patient:

a) Lower border for anterior and posterior fields
   - bottom of obturator foramen.
   - If the lower half vagina was involved, this was marked and the lower border of the field was placed 2 cm below the mark for Cobalt 60 machine and 1 – 2 cm below the mark for linear accelerators (Figure 4).

b) Upper border for anterior and posterior fields – Mid L5 (Figure 4).

c) Lateral borders 1.5 – 2 cm beyond pelvic rim, unless the lower ⅓ of the vagina was involved. Inguinal nodes treated to beyond acetabulum margin (Figure 4).

d) Posterior margin for lateral fields (Figure 5).

- IB2 – IIB proximal – bottom S3.
- IIB distal (outer half of parametria involved) – IIIB entire anterior sacrum.

e) Anterior margin lateral fields (Figure 5).

- top of pubic symphysis.

The entire treatment was to be completed in 6 to 7 weeks. High dose rate brachytherapy (HDR) was given concurrently during the final weeks of external beam, and not on the same day as chemotherapy.

FIGURE 4

AP/PA SIMULATION FILM

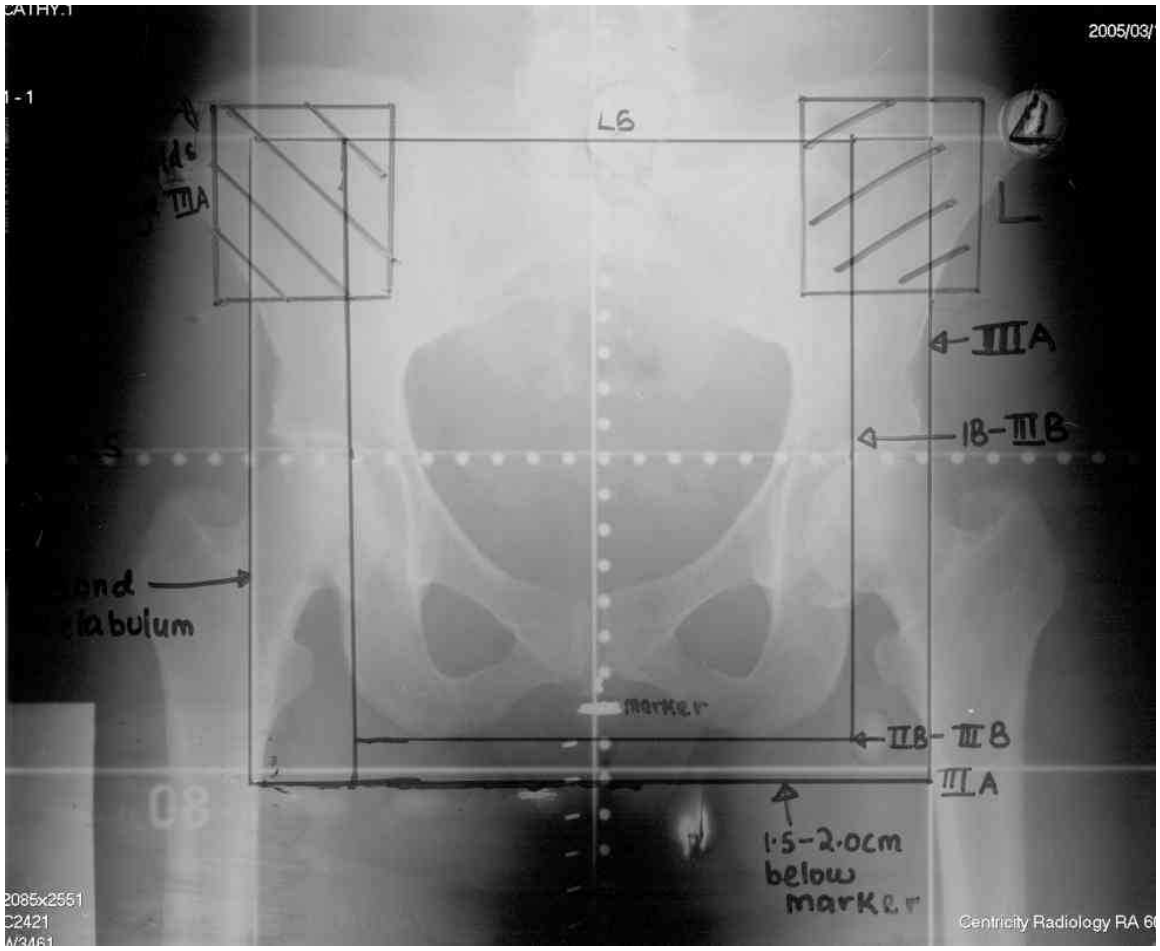
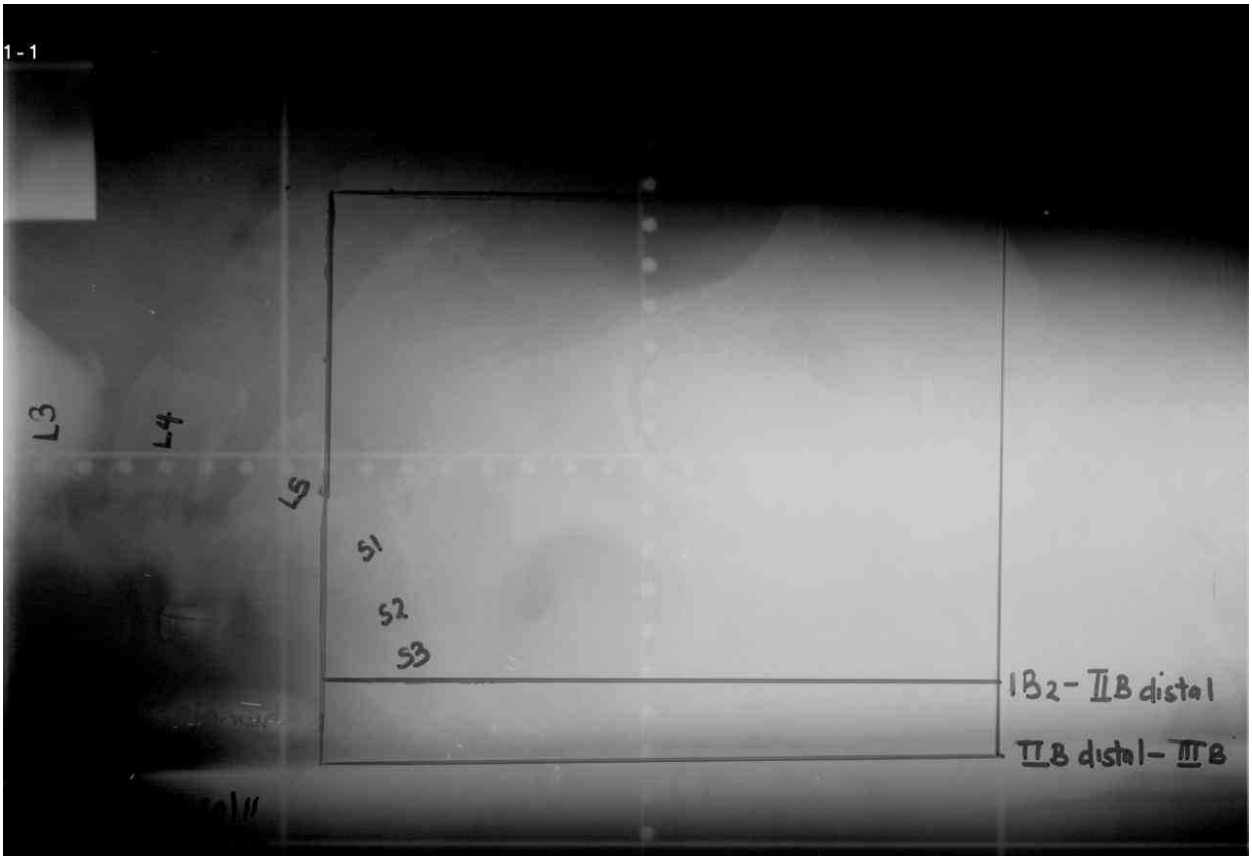


FIGURE 5

LATERAL SIMULATION FILM



Chemotherapy

Cisplatin was administered for 6 weeks on the first day of every radiotherapy week, normally a Monday, unless a public holiday. Cisplatin was administered, as a short intravenous infusion over a period of a ½ hour to 2 hours, in 1000 ml of 0.9% NaCl. The patients were pre-hydrated with 1 litre of normal saline together with calcium gluconate 10 ml, $MgSO_4$ 1 g/L and KCl 20 meq/L. Prophylactic anti-emetics consisted of Dexamethasone (8 mg I.V) and Ondansetron (Zofran) 8 mg I.V. Groups consisting of 3 patients each were treated at each of the 3 pre-determined dose levels (20, 25, and 30 mg/m^2) and no intrapatient dose escalation was

permitted. Thedose was escalated for the next group after all 3 patients at the previous dose level had completed at least 6 cycles of chemotherapy. The doses of Cisplatin were based on the body surface area. Bone marrow-stimulating growth factors, such as erythropoetin, and colony stimulating growth factors were not used.

Evaluation of Toxicity

Chemotherapy toxicity was graded using the CTC (Common Toxicity Criteria) method formulated by the NCI (National Cancer Institute).[70] Toxicity, ECOG status and biochemical profile was assessed, prior to each chemotherapy cycle. Full blood counts and clinical assessments were performed weekly during all treatment cycles. Tables 4.3, 4.4, 5.0 and 5.1 (Appendix).

DLT (Dose Limiting Toxicity) was defined as grade IV neutropenia, grade IV thrombocytopaenia, complicated grade III haematologic toxicity (neutropaenia with fever, thrombocytopaenia with bleeding requiring platelet transfusion); grade III/IV non-haematological toxicity, other than nausea and vomiting (Table 3.0).

The MTD was defined as the most dose intensive regimen with acceptable toxicity, namely, less than 1 out of 3 or 2 out of 6 patients experiencing a DLT.

A reduction in creatinine clearance to less than 60 m/min was also viewed as a DLT, although it does not form part of the CTC criteria. This is based on the fact that creatinine clearance has to be calculated before administration of Cisplatin. Entry criteria mandated serum creatinine

within normal limits for the NCI of Canada, or not greater than 2.0 mg/dl in the GOG 123, and treatment with Cisplatin was withheld where the creatinine clearance fell to less than 50 ml/min.

Cockcroft & Gault Formula 1976, 1992[71,72]

Cockcroft & Gault reviewed the hospital records of 249 male patients, which contained at least two 24-hour creatinine clearance measurements, and which measurements did not vary by more than 20%. The serum creatinine in a fasting blood sample was estimated. They plotted the mean 24-hour creatinine excretion/kg body weight for 7 different age groups (varying in age between 18 and 92) against the mean age of the respective groups. Linear regression was applied to the mean values and resulted in the widely used Cockcroft-Gault formula. The methodology used by Cockcroft and Gault has, however, been criticized as only data relating to males was used. The use of a factor of 0.85 to allow for the difference in mass between males and females in extrapolating estimates for females was based on expert opinion only, and not on actual data.

Creatinine clearance is a more effective way of assessing renal function than serum creatinine. The use of endogenous serum creatinine to assess renal function is simple and is widely accepted. A limiting factor, however, is that creatinine is not filtered by the glomerulus alone, but is also secreted by the renal tubular cells. The rate of secretion by the renal tubular cells is highly variable and is individual specific and time specific. This may lead to inaccurate prediction of GFR. The serum creatinine concentration also depends on lean body mass (muscle), which varies according to age and body size (as assessed by body weight) and sex.

The Cockcroft-Gault formula is widely used by clinicians to estimate the GFR by calculating the creatinine clearance from the serum creatinine. The factors required for this calculation are readily accessible, namely, serum creatinine, age, weight and gender of the individual. The formula takes into account the effects of progressive decline in muscle mass in ageing adults as well as variations in muscle mass between males and females, on creatinine production.

Cockcroft & Gault Formula for females[71, 72]

Creatinine measured in µmol/l

$$\text{Creatinine Clearance} = \frac{[140 - \text{Age}] \times \text{Weight} \times 1.02}{\text{Serum Creatinine}}$$

The weight is measured in Kilograms (Kg), age in years and creatinine clearance in mls/min.

The determination of biochemical creatinine by 24-hour urine creatinine collection provides a more accurate estimation of GFR than serum creatinine concentration alone, but it is often inconvenient for patients and the results cannot always be relied upon. 24-hour urine collection is problematical, for example, inaccurate urine collections, uncooperative patients and the need for indwelling catheters cause delays in diagnosis and the dose modification of nephrotoxic drugs. Practically, creatinine results are only available, at best, 12 hours, and more often between 24 to 36 hours after completion of urine collections. Other more practical methods are accordingly preferred. In order to quickly assess the GFR, the Cockcroft and Gault formula is preferred.

In this study, a calculated creatinine clearance was used, rather than GFR. It is strongly considered that creatinine clearance should be deemed to be dose limiting toxicity. The cut off

for creatinine clearance at which Cisplatin is to be given was chosen to be 60 ml/min, because most studies use this cut off. Reed recommends that caution should be exercised if the 24-hour creatinine clearance is less than 60 mL/min, and that alternative chemotherapeutic agents should be used in these circumstances.[15] As this was a phase I trial, doses were not reduced or escalated in individual patients.

Labeled compounds, such as Chromium – 51 ethylene diaminetetraacetic-acid {(^{51}Cr) EDTA} and Technicium – 99 m diethyltriaminepentaaceticacid (Tc^{99}m DTPA), have been developed as GFR markers. These radiolabeled compounds expose patients to radiation, are expensive and are not readily available.

Treatment Modifications

Cisplatin was discontinued, if a patient developed significant ototoxicity (grade > 1), neurotoxicity (≥ grade 3), renal abnormalities ≥ grade 3 or any other non-haematological grade III/IV toxicity, other than nausea and vomiting. In addition, Cisplatin was discontinued if the creatinine clearance dropped to < 60 ml/min.

Statistical Considerations

This study was designed to evaluate the acute toxicities of this treatment regime. Descriptive data analyses were used as the primary statistical analysis tool, to report demographics and adverse events.

Criteria for Response

All responses were measured clinically. Responses to therapy were classified as complete, or incomplete. A complete response was defined as the complete disappearance of all gross disease for at least 6 weeks after completion of the therapy. Incomplete response was defined as the presence of disease based on physical examination findings. Progressive disease was defined as an increase in tumour size, or the appearance of any new lesion, after initiation of the therapy. Due to limited resources, radiological investigations to assess the responses, in accordance with WHO criteria, were not done.

TABLE 3.0

Dose limiting toxicity (DLT)

Toxic response	**Dose limiting toxicity**
Neutrophil count	Grade 4 toxicity or complicated grade 3 neutropaenia with fever
Platelet count	Grade IV toxicity or complicated grade III thrombocytopaenia with bleeding requiring platelet transfusion
Non haematologic toxicity, other than nausea and vomiting	Grade III/IV

4.0 RESULTS

Patient Characteristics

19 patients participated in the study. One patient was excluded, after 3 cycles of chemotherapy due to withdrawal of consent. The characteristics of the remaining 18 patients are shown in Table 3.1.

All patients presented with an ECOG status of 0 or 1. 4 patients did not complete chemotherapy due to low creatinine clearance. The planned radiotherapy treatment was completed for all patients within an average of 37 days (range between 33 to 41 days). 88.8% of the patients completed the treatment within 37 days. There were no treatment delays as a result of haematological, neurological or gastrointestinal toxicity. There were some short treatment delays for particular patients due to personal reasons.

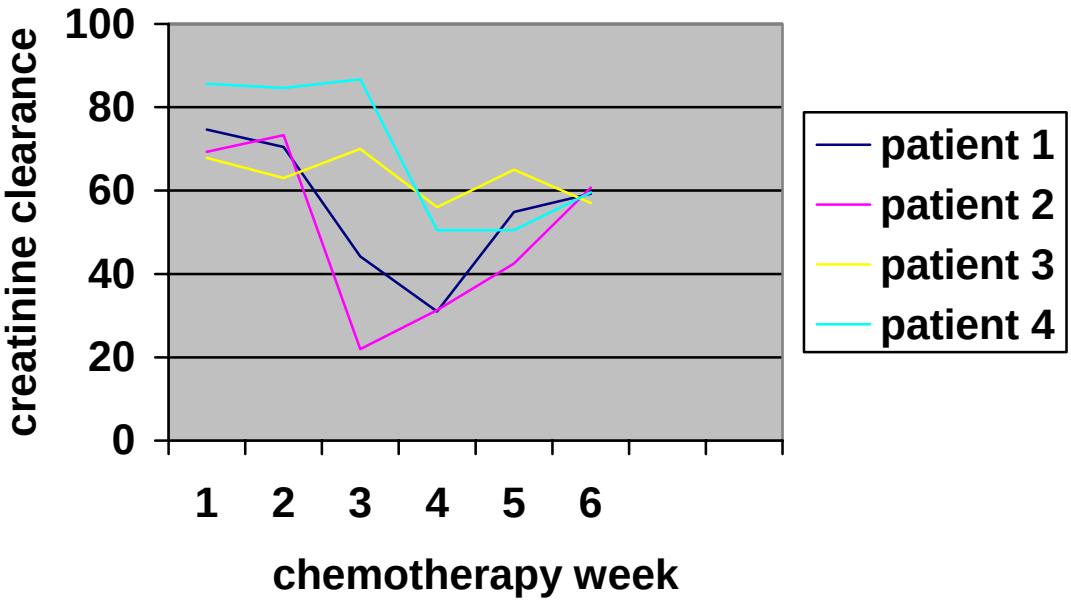
Treatment Delivery, Toxicity, MTD

Treatment delivery is summarized in Tables 3.2 and 3.3. The toxicity observed is summarized in Tables 3.4, 3.5 and 3.6. Severe toxicity mainly manifested itself as raised serum creatinine with low calculated creatinine clearance. This was noted only at dose level III. Grade 2 anaemia was noted only in one patient at dose level III. No grade 3 gastrointestinal or neurological toxicity was noted. There were no cases of febrile neutropaenia and no auditory toxicity.

Grade 2 toxicity, with elevated serum creatinine, was noted in 2 patients at dose level III. These two patients were 50 and 46 years old, with FIGO stage IIIB and IB2 carcinoma of the cervix, respectively. The absolute serum creatinine values were 168 μmol/ml and 174 μmol/ml respectively. The renal function in these 2 patients deteriorated rapidly after only two cycles of Cisplatin. Chemotherapy was not reinstated at that stage. The corresponding creatinine clearances were 31 ml/min and 22 ml/min, respectively. This was regarded as a DLT. The DLT was, however, reversed after discontinuation of the chemotherapy and it normalized by the 6^{th} week of treatment.

The other 2 patients, whose renal function deteriorated at dose level III, had creatinine clearances of 56 and 50.5 ml/min, respectively. The renal function of these 2 patients deteriorated during week 4 of the treatment. They were 46 and 61 years old and both had FIGO stage IIB carcinoma of the cervix. The calculated creatinine clearance of one of these patients improved from 56 ml/min to 65 ml/min by the 5^{th} week of treatment, but deteriorated again after the 4^{th} cycle of chemotherapy and had not recovered fully by the end of treatment and, therefore, no further chemotherapy was administered. The renal function of the other patient, with a calculated creatinine clearance of 50.5 ml/min during week 4 of treatment, had normalized by the last week of treatment (Figure 6 below).

Figure 6- Renal toxicity



Grade 2 leucocytopaenia was noted at all dose levels. Grade 2 neutropaenia occurred in 1 patient at dose level I and in the other patient at dose level III. No grade 3 or 4 haematological toxicity was noted at any of the dose levels. Grade 2 hypomagnesaemia occurred in 1 patient at dose level III.

Efficacy

Overall 16 complete responses and 1 partial response were recorded 6 weeks post treatment. One patient's response could not be evaluated, as the patient did not return for examination after her last treatment. To date, 16 out of the 18 patients, who participated in this study, are still alive. One patient died of hepatic failure one year after participating in this study,

probably from suspected liver metastasis, as seen on the patient's abdominal sonar report. Another patient died from a pelvic recurrence two years after participating in this study. Both patients had completed all 6 cycles of chemotherapy at dose level III and I (30 mg/m^2 & 20 mg/m^2), respectively, and had had stage IIB cancer of the cervix.

TABLE 3.1

Patient characteristics (n = 18)

Characteristics	**Number of patients**
Number of Patients	18
Age (years)	
Median	47
Range	39 – 68
Race (African: White: Mixed race)	15:2:1
FIGO Stage	
IB2	5
IIB	10
IIIB	3

TABLE 3.2

Dose level & number of patients accrued

Level	**Dose of Ciplatin (mg/m^2)**	**Evaluable for DLT[a]**	**Developing DLT[a]**
I	20	3	0
II	25	3	0
III	30	12	4

[a]*Dose-limiting toxicity*

TABLE 3.3

Treatment delivery

Chemotherapy cycles	**No. of patients**		
	Level I n=3	Level II n=3	Level III n=12
6	3	3	8
5	0	0	0
4	0	0	2
3	0	0	0
2	0	0	2
1	0	0	0

TABLE 3.4

Toxicity at Dose Level I Cisplatin 20 mg/m^2/wk (n=3)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	16	1	1	0	0
Nausea	11	7	0	0	0
Vomiting	16	0	2	0	0
Elevated creatinine	12	6	0	0	0
Creatinine clearance	18	0	0	0	0
Leucocytopaenia	9	2	7	0	0
Neutropaenia	13	4	1	0	0
Febrile neutropaenia	18	0	0	0	0
Thrombocytopaenia	17	1	0	0	0
Neuro-motor	18	0	0	0	0
Neuro-sensory	18	0	0	0	0
Auditory	18	0	0	0	0
Hypomagnesaemia	18	0	0	0	0
Hypocalcaemia	18	0	0	0	0

Note: patients could have more than one complication.

TABLE 3.5

Toxicity at Dose Level II Cisplatin 25 mg/m^2/wk (n=3)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	10	8	0	0	0
Nausea	13	5	0	0	0
Vomiting	18	0	0	0	0
Elevated creatinine	17	1	0	0	0
Creatinine clearance	18	0	0	0	0
Leucocytopaenia	17	0	1	0	0
Neutropaenia	18	0	0	0	0
Febrile neutropaenia	18	0	0	0	0
Thrombocytopaenia	18	0	0	0	0
Neuro-motor	18	0	0	0	0
Neuro-sensory	18	0	0	0	0
Auditory	18	0	0	0	0
Hypomagnesaemia	18	0	0	0	0
Hypocalcaemia	18	0	0	0	0

Note: patients could have more than one complication.

TABLE 3.6

Toxicity at Dose Level III Cisplatin 30 mg/m^2/wk (n = 12)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	61	8	3	0	0
Nausea	35	36	1	0	0
Vomiting	60	4	8	0	0
Elevated creatinine	63	7	2	0	0
Creatinine clearance	60	0	0	12	0
Leucocytopaenia	56	12	4	0	0
Neutropaenia	69	3	0	0	0
Febrile neutropaenia	72	0	0	0	0
Thrombocytopaenia	67	5	0	0	0
Neuro-motor	72	0	0	0	0
Neuro-sensory	72	0	0	0	0
Auditory	72	0	0	0	0
Hypomagnesaemia	67	4	1	0	0
Hypocalcaemia	71	0	1	0	0

Note: patients could have more than one complication.

TABLE 4.0

Objective responses

Dose level	n	CR	PR	SD	PD	NE
Level I	3	3	-	-	-	-
Level II	3	3	-	-	-	-
Level III	12	10	1	-	-	1

CR = Complete Response

PR = Partial Response

SD = Stable Disease

PD = Progressive Disease

NE = Not Evaluable

n = Number of Patients

5.0 DISCUSSION

This phase I study was performed to assess, in patients with cancer of the cervix, the safety of, and to determine the MTD of, Cisplatin when administered weekly, concurrently with radical pelvic irradiation. Overall, the study demonstrates that this combination is fairly well tolerated by patients, and that no unexpected toxicities were observed beyond those generally associated with single agent Cisplatin.

The use of the optimal chemotherapy schedule (multi-drug, single drug and the optimal dose of Cisplatin) in combination with pelvic radiotherapy is still controversial. Several phase I & II trials have suggested a potential benefit of concurrent Cisplatin chemotherapy and pelvic irradiation treatment in patients with locally advanced cervical cancer.[53,54, 56] In these studies the dose of weekly Cisplatin ranged from 10 mg/m^2 to 30 mg/m^2. In a phase III study by Piver et al,[58] it was found that Cisplatin at 1mg/kg (maximum weekly dose of Cisplatin 60 mg) was a more tolerable regimen than the higher dose of Cisplatin100 mg/m^2 administered every 4 weeks.

5 of the 6 most recently reported studies proved the superiority of concurrent Cisplatin based chemotherapy and radiotherapy, over the use of radiotherapy alone, in treating invasive cancer of the cervix.[4,5,6,7,8,9] 3 of these studies, namely, GOG 120, GOG 123 and NCI of Canada,[4,5, 7] used Cisplatin doses of 40 mg/m^2 weekly. The study by GOG 120[4] demonstrated that the use of Cisplatin on its own was equivalent to the use of Cisplatin combined with 5-FU, with the latter regimen having greater toxicity. Based on these studies, a combination of weekly 40

mg/m^2 Cisplatin and radiotherapy has been adopted as a standard component of treatment in most centres. Experience with this treatment regimen, however, is still limited outside of clinical studies. The maximum weekly dose of Cisplatin should be 70 mg.[4,52]

A review of current literature on the topic did not reveal any phase I studies proving that Cisplatin 40 mg/m^2 weekly is the maximum tolerated dose. From the literature it appears that Cisplatin administration at 1 mg/kg weekly is equivalent to Cisplatin 40 mg/m^2 weekly (the maximum weekly dose of Cisplatin being 60-70 mg).

Adequate renal function was an eligibility criteria for all patients participating in the clinical trials using Cisplatin. In a phase I study reported by Twiggs,[53] Cisplatin was withheld because of transient rises in BUN and creatinine. In a phase I/II study reported by Malfetano,[56] Cisplatin was discontinued if the creatinine exceeded 2.0 mg %. In further phase III studies, including the NCI of Canada and the GOG 120,[5,4] Cisplatin was discontinued, if the serum creatinine exceeded 140 μmol/ml (2.0 mg /dl). In a study from Roswell Park, reported by Lele,[73] patients received Cisplatin only if the urine creatinine clearance was greater than 60ml per min. In this particular study one patient developed a drop in creatinine clearance to 30ml per min. The serum creatinine of this patient also rose to 1.7 mg % and Cisplatin was discontinued. In two other studies, reported by Serkies and Wong,[52,61] Cisplatin was discontinued if creatinine clearance fell to <50 ml /min.

In this study, a DLT was observed at a Cisplatin dose of 30 mg/m^2. The DLT consisted of elevated serum creatinine and low calculated creatinine clearance. Although most studies do

not use GFR as a DLT, it was felt to be justified in this study, as chemotherapy could not be given when the creatinine clearance was low.

Other side effects observed were mild and included, diarrhoea, nausea, vomiting, hypomagnesaemia, thrombocytopaenia, leucopaenia and neutropaenia. These spontaneously regressed upon discontinuation of the chemotherapy.

Given that the DLT was 30 mg/m^2, the MTD was taken as 25 mg/ m^2. This is lower than doses used in other studies, for example, GOG 120, GOG 123 and NCI of Canada,[4,5, 7] which used 40 mg/m^2. Those studies did not report on the exact number of patients who, developed renal abnormalities, if any. They also did not report in how many patients the Cisplatin dose was modified or discontinued.

In this study, Cisplatin was administered, as a short intravenous infusion over a period of a ½ hour to 2 hours, in 1000 ml of 0.9% NaCl. The patients were pre-hydrated with 1 litre of normal saline together with calcium gluconate 10 ml, $MgSO_4$ 1 g/L, KCl 20 meq/L. There was no post chemotherapy hydration.

Based on the findings of this study, post chemotherapy hydration may be necessary even at these low doses of Cisplatin. Creatinine clearance should be obtained both at baseline and before each cycle of Cisplatin chemotherapy. Renal function (Urea and Creatinine) as well as serum electrolytes (Na, Mg, Ca and K) should be monitored carefully during treatment. The fluid status of the patient is critical. The recommended approach is to give at least 1 litre before, and 1 litre after Cisplatin treatment of 0.9 % sodium chloride with 20 mEq of KCL.

With higher doses of Cisplatin more aggressive hydration should be considered, with at least 2 litres of fluid administered before the treatment. Urine output should be greater than 100 ml per hour. Furosemide diuresis may be used after every 2 litres of fluid.[29]

The patients, who participated in this study may have reduced tolerance to higher doses of Cisplatin, due to inherent renal dysfunction. Other factors that could potentially increase nephrotoxicity may be patient related, drug related or related to drug interactions. Patient factors include, age, race, previous renal insufficiency, advanced stage cancer, concurrent sepsis, dehydration and volume depletion.

Despite the fact that all the patients responded to the treatment, further follow up is required to assess the overall response rate and survival. The effectiveness of doses of Cisplatin less than 40 $mg/m^2/wk$ needs to be studied.

Table 4.1 illustrates that the patients in this study experienced greater haematological, gastrointestinal and renal toxicity at all the dose levels than the patients in the other three trials. Of note was the unexpectedly high incidence of leucocytopaenia at dose level I, as compared to higher dose levels. Renal toxicity was not a reason for ceasing treatment in those studies, whereas in this study renal toxicity was dose limiting. Anaemia, granulocytopaenic fevers and thrombocytopaenia were not common, either in this study or those other studies. There were no treatment delays for neutropaenia.

Direct comparisons between this and other studies are, however, difficult because of the differences in the chemotherapeutic regimens, radiotherapy administered and the presence or absence of prior surgery.

The planned radiotherapy treatment was completed for all patients within an average of 37 days (range between 33 to 41 days). 88.8% of the patients completed the treatment within 37 days. The overall treatment times in the study were shorter than those in most other trials. For instance, in the GOG 120, GOG 123 and NCI of Canada trials, the overall treatment times were 63, 50 and 48 days, respectively.[4, 5, 7] The treatment delay may have resulted from the higher doses of Cisplatin used in those trials.

TABLE 4.1

Moderate and severe toxicity of combined treatment in comparison to other trials[4,5,7]

Toxicity	**Reference**					
	RT+CDDP+ Hysterectomy GOG 123 n = 183	RT+/- CDDP NCI of Canada n = 127	RT+/- CDDP GOG 120 n = 176	RT+CDDP This study Dose level **I** n = 3	**II** n = 3	**III** n = 12
Thrombocytopaenia	-	-	1	-	-	-
Leucocytopaenia	-	-	13	40	6	6
Anemia	-	-	-	-	-	1
Granulocytopaenia	-	-	-	6	6	-
Low calculated Cr. Cl.	-	-	-	-	-	17
Neurological	1	2	1	-	-	-
Diarrhoea (%)	-	-	-	6	-	4
Nausea	-	-	-	-	-	1
Vomiting (%)	-	-	-	11	-	11

Moderate toxicity represents grade 2 (requiring only conservative treatment) and severe toxicity represents grade 3 (requiring more aggressive treatment).

Note: patients could have more than one complication.

TABLE 4.2

Cisplatin cycles delivered in this study as compared to the Polish study[52]

Chemotherapy cycles	No. of patients (%)			
	Level I Cisplatin 20 m^2 weekly n = 3	Level II Cisplatin 25 m^2 weekly n = 3	Level III Cisplatin 30 m^2 weekly n = 12	Polish study Cisplatin 40 m^2 weekly n = 112
6	3	3	8(66.6)	7(6.2)
5	0	0	0(0)	43(38.4)
4	0	0	2(16.6)	33(29.5)
3	0	0	0(0)	15(13.4)
2	0	0	2(16.6)	6(5.4)
1	0	0	0(0)	8(7.1)

Table 4.2 compares the Cisplatin cycles delivered in this study with the Polish study.[52] In this study at dose level III 30 mg/m^2, only 66.6% of the patients received the planned 6 cycles of Cisplatin. These results are similar to those reported by the GOG 120, NCI of Canada, GOG 123 and the Polish trial.[4, 5,7, 52] In the GOG 120 study, 93% of the patients received at least 4 cycles of Cisplatin, and 49% received at least 6 cycles of Cisplatin. Similarly, in the GOG 123 trial, 90% of the patients received at least 4 courses of Cisplatin. In the NCI of Canada study, 86% of patients assigned to the chemoradiotherapy group received at least 5 cycles of Cisplatin. In the Polish study, 74% of the patients received at least 4 cycles of Cisplatin, but

full, planned chemotherapy was administered to only 45% of the patients. Not all the patients completed chemotherapy in the majority of trials.

6.0 CONCLUSION

The recommended dose of Cisplatin is 40 mg/m^2/wk given concurrently with pelvic radiotherapy. This regimen can be delivered on an outpatient basis. In a number of patients, however, early toxicity precludes delivery of the full planned chemotherapy dose. Cisplatin-induced nephrotoxicity was found to be dose limiting in this study, as well as in other clinical trials.

In this study, a DLT was observed at a Cisplatin dose of 30 mg/ m^2. The DLT consisted of elevated serum creatinine and low calculated creatinine clearance. This study demonstrates that a dose of 25 mg/m^2 weekly of Cisplatin is the maximum tolerated dose, when used in combination with pelvic irradiation, for this group of patients. This regimen is tolerable with few side effects. It is unclear from this study whether improved hydration of the patients, prior to and after delivery of the chemotherapy, will lead to an improvement in tolerance. This needs to be tested in future studies.

Based on this study it is impossible to comment on whether the lower dose of Cisplatin is as effective as a dose of 40 mg/m^2. More patients need to be evaluated and follow up procedures conducted over a longer period of time in order to assess this factor.

The patients in this study may have reduced tolerance to higher doses of Cisplatin, when compared to Western patients, due to the following factors, which are prevalent in developing countries:

- Inherent renal dysfunction
- Advanced stage cancer
- Chronic infections
- Dehydration and volume depletion
- Drug related factors
- Limited medical facilities

1. Inherent renal dysfunction:

Chronic renal failure is a common pathology. Many patients with cancer develop renal fluid and electrolyte complications during the course of their disease. These disorders may be part of the basic manifestations of the malignancy, or may result from vigorous multi-modal cancer treatment.[80] Chronic renal insufficiency is often progressive, even if the initiating factors are no longer present.

2. Advanced stage cancer

The patients in this study presented with advanced stage cancer that may lead to obstructive nephropathy and metastatic infiltration. Malignancy manifestations such as, disseminated intravascular coagulation, amyloidosis, electrolyte abnormalities and the syndrome of inappropriate ADH secretion contribute to renal failure in patients with advanced cancer. Patients with advanced cancer have a high tumour burden and acute

renal failure may occur after administration of chemoradiotherapy, due to tumour lysis syndrome.

3. **Chronic infections**

Patients may suffer from underlying chronic infections, for example, pyelonephritis, tuberculosis, HIV and pelvic inflammatory diseases, which predisposes them to renal abnormalities.

4. **Dehydration and volume depletion**

These patients have limited access to fluids. They travel long distances to hospital and stand in long queues before they finally get treatment. Diarrhoea and vomiting during treatment leads to volume depletion and eventually to renal dysfunction. Mild dehydration induces an increase in vasopressin secretion, which in turn leads to morphologic and functional changes in the kidney leading to acute renal failure. Diarrhoea and vomiting also lead to renal failure due to intravascular volume depletion.

5. **Drug related**

Most patients are on chronic pain medication usually consisting of non-steroidal anti-inflammatories (NSAIDS) such as ibuprofen (Brufen®) and analgesics such as paracetamol (Panado®) which are potentially nephrotoxic drugs.

6. **Limited medical facilities**

   Due to limited resources, the public hospitals cannot provide enough fluids and anti emetics to cope with problems of volume depletion in these patients. Patients cannot access cold drinks easily, due to financial constraints.

Careful attention must be given to radiotherapy details including, the dose and duration of delivery, the use of brachytherapy, whenever possible, and adequate doses of Cisplatin chemotherapy given concurrently with radiation therapy. All these are important factors that affect the prognosis of patients with carcinoma of the cervix.

7.0 RECOMMENDATIONS FOR FUTURE RESEARCH

This dissertation has highlighted the following recommended areas for future research:

1. Further dose finding studies in the sample population group appear to be warranted.
2. Further study is required to determine whether Cisplatin doses of 25 mg /m^2 are as effective as the standard 40 mg /m^2 doses with less toxicity.
3. Novel and effective synergistic systemic agents should be researched. These agents include, taxanes (paclitaxel and docetaxel) and topoisomerase I inhibitors (topotecan and irinotecan). Phase I and II trials suggest that these agents are active against advanced and recurrent cervical cancers.[76]

Hopefully, the vast array of molecular targetted therapies currently being developed will eventually render the treatment of cervical cancer much more successful.[77, 78,81] These include:

A. The proto-oncogenes E6 and E7 from the virulent HPV 16 and 18, respectively, have been implicated in the pathogenesis of cervical cancer. These proto-oncogenes form complexes with the tumour suppressor genes p53 and retinoblastoma gene (Rb) resulting in immortalization of keratinocytes. These genetic alterations are potential targets for gene therapy.

B. Matrix Metalloproteinase (MMP) degrades the structural extracellular matrix proteins leading to increased invasiveness and metastases. MMP – 1 is associated with the increased risk of lymph node metastases and poor prognosis. Studies are currently evaluating the role of MMP inhibitors.

C. Monoclonal Antibodies against epidermal growth factor receptors (EGFR). The epidermal growth factor receptor (EGFR) family consists of four similar receptor tyrosine kinase (RTK) transmembrane proteins, which include EGFR1– 4. Most solid epithelial tumours over express EGFR – 1 on their surface. Cetuximab is a chimeric monoclonal antibody directed against EGFR – 1 and has shown promising results in the treatment of other epithelial tumours including head and neck and colorectal cancer.

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9.0 APPENDIX 1

TABLE 4.3

CTC Haematological toxicity

Toxicity	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
HB g/dl	12.1-16.3	<12.1-10	8-<10	6.5-<8	<6.5
WBC x10^9/l	3.92-9.88	<3.92-3	≥2-<3	≥1-<2	<1
PLT x10^9/l	178-400	<178-75	≥50-<75	≥10-<50	<10
Neutrophil x10^9/l	2.0-7.5	≥1.5-<2	≥1.0-<1.5	≥0.5-<1.0	<0.5
Febrile Neutropenia absolute neutrophil count <0.5 x10^9/l fever ≥38.5^{0}c	None	None	None	Present	Life threatening sepsis

TABLE 4.4

Gastrointestinal Toxicity

Adverse event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	None	<4 stools per day	4-6 stools per day	≥7 stools per day	Physiologic consequence requiring intensive care or haemodynamic collapse
Nausea	None	Able to eat	Oral intake significantly decreased	No significant intake requiring IV fluids	-
Vomiting	None	1 episode per day	2-5 episodes per day	≥6 episodes per day	Require parenteral nutrition or intensive care or haemodynamic collapse

TABLE 5.0

Neurological toxicity

Adverse event	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Neuropathy-motor	Normal	Subjective weakness but no objective findings	Mild objective weakness interfering with function ,but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Neuropathy-sensory	Normal	Loss of deep tendon reflexes or parasthesia, but not interfering with function	Objective sensory or parasthesia interfering with function, but not interfering with activities of daily living	Sensory loss or parasthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
Auditory/ Hearing	Normal	Mild	Moderate	Severe	Life threatening or disabling

TABLE 5.1

Renal/genitourinary toxicity

Adverse event	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine μmol/L	60-100	>100-<=150	>150-<=300	>300-<=600	>600
Calcium mmol/L	2.05-2.56	<2.05-2.0	1.75-<2.0	1.5-<1.75	<1.5
Magnesium mmol/L	0.65-1.10	<0.65-0.5	0.4-<0.5	0.3-<0.4	<0.3
Albumin g/L	35-52	<35-30	≥20-<30	<20	-

10.0 APPENDIX II

Abbreviations

CDDP	Cis-Diamine-Dichloro-Platinum (Cisplatin)
CR	Complete Response
CTC	Common Toxicity Criteria
DLT	Dose Limiting Toxicity
ECOG	Eastern Co-operative Oncology Group
FIGO	International Federation of Gynecology and Obstetrics
5-FU	5-Fluorouracil
GFR	Glomerular Filtration Rate
GIT	Gastrointestinal Tract
GOG	Gynecology Oncology Group
Gy	Gray
HB	Haemoglobin
HDR	High Dose Rate
HU	Hydroxyurea
HPV	Human Papilloma Virus
Linac	Linear Accelerator
MTD	Maximum Tolerated Dose
n	Number of Patients
NE	Not Evaluable
PD	Progressive Disease
PR	Partial Response

RT	Radiation Therapy
RTOG	Radiation Therapy and Oncology Group
SD	Stable Disease
Sq. Cell	Squamous Cell
SWOG	South West Oncology Group
WBC	White Cell Count