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Clinical implications of gemcitabine in the treatment of cervical cancer

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ABSTRACT

Overall, cervical carcinoma is the seventh most frequent malignancy and the second most common cancer among women, with an estimated 493,000 new cases and 274,000 deaths recorded in 2002. In the last few years significant advances in the management of this cancer have been achieved, including confirmation that a combination chemotherapy regimen containing cisplatin is superior in terms of overall survival than single-agent cisplatin for treating metastatic or recurrent disease. Likewise, for localised advanced disease, cisplatin-based concurrent chemoradiation has been proven to be superior to radiation treatment alone. This review analyses data from trials that have investigated gemcitabine either alone or in combination with cisplatin for treating metastatic and recurrent disease, as well as the use of radiation and cisplatin for locally advanced disease.

1. Introduction

According to Globocan 2002, cervical carcinoma is the seventh most common cancer overall and the second most common in women, with an estimated 493,000 new cases and 274,000 deaths recorded in 2002. This neoplasia occurs much more frequently in developing countries, where 83% of the cases arise. Cervical cancer accounts for 15% of female cancers in the developing world, with a 1.5% risk of developing the disease before 65 years of age. In developed countries, cervical cancer accounts for only 3.6% of new cancers, with a cumulative risk of 0.8% [1].

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2. Current standard of treatment

The treatment of cervical cancer is driven by its stage, and, in terms of treatment, can be divided into three main groups [2]:

(I) Early stages: IA1 (International Federation of Gynecology and Obstetrics [FIGO]) – treated by local procedures such as conisation or extrafascial hysterectomy; IA2–IB1 (FIGO) – treated by radical hysterectomy or radiation therapy if the surgical procedure is medically contraindicated.
(II) Locally advanced (FIGO) stages IB2–IVA – treated with concurrent cisplatin-based chemoradiation.
(III) IVB and recurrent local or systemic disease (FIGO) – in which palliative combination chemotherapy based on cisplatin is the current standard of treatment.

Treatment with systemic chemotherapy for metastatic, recurrent or persistent disease is disappointing. In

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general, response rates are low and typically short-lived and, therefore, do not affect progression-free and overall survival greatly. Thus, chemotherapy has a palliative role in these patients.

Approximately 50 chemotherapy drugs have been evaluated as single agents for treating advanced or recurrent cervical carcinoma. Since 1985, single-agent cisplatin (50 mg/m^2) was considered the standard against which experimental regimens were compared [3]. However, a recent phase III comparison of cisplatin versus cisplatin plus topotecan in the Gynecologic Oncology Group (GOG)-179 study showed that the combination had statistically superior outcomes, with median overall survival of 9.4 versus 6.5 months ($P = 0.017$), median progression-free survival (PFS) of 4.6 versus 2.9 months ($P = 0.014$), and response rates of 27% versus 13% [4]. This study was the first to show a statistically significant impact on overall response rate, median PFS and median survival, with all outcome measures favouring the two-drug regimen. Therefore, cisplatin plus topotecan could now be considered the standard therapy. Despite these encouraging results, most responses are partial and of short duration, which underlines the need for novel combinations.

3. Gemcitabine in the management of metastatic, persistent or recurrent disease

3.1. *Single-agent gemcitabine*

Gemcitabine is a deoxycytidine analogue that inhibits DNA synthesis [5]. Early studies showed that gemcitabine exhibits cytotoxic activity against a broad range of cancer cell lines *in vitro* and in animal models, including human cancer xenografts [6,7], as well as in several solid tumours, either alone or combined with cisplatin [8]. Gemcitabine is active against several cervical carcinoma cell lines [9]. In a clinical setting, four studies of single-agent gemcitabine using a 28-day schedule of 3 weeks of treatment at doses of 800–1250 mg/m^2 with 1 week rest have been reported in this disease. In 107 evaluable patients, response rates were unimpressive (0–11%); however, disease stabilisation and symptom improvement were achieved in a large proportion of patients with negligible toxicity [10–13]. These results demonstrate the antitumour activity of single-agent gemcitabine in this setting.

3.2. *Gemcitabine plus cisplatin combination*

The known synergy between gemcitabine and cisplatin [14] led to the combination being tested in patients with advanced or recurrent cervical carcinoma. In a phase I/II study of cisplatin plus gemcitabine delivered to 28 women with recurrent, previously radiated cervical carcinomas, chemotherapy was given on a 28-day cycle: cisplatin (50 mg/m^2) on day 1 and gemcitabine (600–1000 mg/m^2) on days 1, 8 and 15. Twenty-seven patients were evaluable for toxicity and disease response. Toxicities were predominantly haematological. The maximum tolerated dose was not reached. One patient had a complete response (CR) and three achieved a partial response (PR) (15% response rate), while 41% had stable disease and disease progressed in 44% of patients. Median survival was 11.9 months [15].

Burnett et al. evaluated this combination in 19 patients using gemcitabine (1250 mg/m^2) on days 1 and 8 and cisplatin (50 mg/m^2) on day 1 every 3 weeks. In 17 evaluable patients, one CR and six PRs were observed, for an overall response rate of 41%. The regimen was well tolerated with only 3.6% of patients having grade IV haematological toxicity [16].

Lorvidhaya et al. enrolled 51 patients with the same schedule but using a higher dose of cisplatin (70 mg/m^2). Among the 40 evaluable patients, three (7.5%) and 27 (67.5%) achieved a CR and PR, respectively, 12.5% had stable disease and the disease progressed in five patients (12.5%). Myelosuppression was the major toxicity. Median time to progression was 8.3 months and median survival was 9.6 months. With a median follow-up of 7.7 months (0.3–22.1 months), 30% of the patients were alive at 12 months [17].

Bouzid and Mahfouf reported results with the same regimen. The overall objective response rates in 57 evaluable patients were 15% and 35% for CR and PR, respectively. One- and two-year survival rates were 44% and 26%, respectively. The combination was well tolerated, with the rate of grade III or higher haematological toxicity being 9% [18].

Other studies include those by Brewer et al. [19], where 32 previously treated patients with squamous cell carcinoma of the cervix were treated with cisplatin (30 mg/m^2) and gemcitabine (800 mg/m^2), and Dueñas-González et al. [20], where a weekly low-dose gemcitabine (100 mg/m^2) plus cisplatin (33 mg/m^2) regimen was assessed in 14 cervical cancer patients (Table 1).

Altogether, these studies indicate that gemcitabine plus cisplatin is active and well tolerated. Based on positive results of the combination of cisplatin and topotecan, the current GOG-204 study compares four cisplatin combinations using topotecan, vinorelbine, paclitaxel or gemcitabine. The results of this study might indicate that the four regimens, while equally effective, may have differences in toxicity and impact on quality of life.

4. Gemcitabine in the management of locally advanced cervical cancer

4.1. *Concurrent chemoradiation*

For nearly 80 years radiation was considered the standard of care. According to the 1998 Annual Report

Table 1 – Gemcitabine and cisplatin for metastatic or recurrent cervical cancer[a]

Authors [ref]	Evaluable patients	Schedule	CR (%)	PR (%)	SD (%)	PFS (median)	OS (median)
Matulonis et al.[15]	27	Gemcitabine 600–1000 mg/m^2 on d 1, 8, 15 every 28 days + Cisplatin 50 mg/m^2 on d 1 every 28 days	3.7	11.1	41	NR	11.9 mo
Burnett et al.[16]	17	Gemcitabine 1250 mg/m^2 on d 1, 8 every 21 days + Cisplatin 50 mg/m^2 on d 1 every 21 days	5.9	35.3	23.5	NR	12 mo* 7 mo#
Lorvidhaya et al.[17]	40	Gemcitabine 1250 mg/m^2 on d 1, 8 every 21 days + Cisplatin 70 mg/m^2 on d 1 every 21 days	7.5	67.5	12.5	8.3	9.6 mo
Bouzid and Mahfouf[18]	40	Gemcitabine 1250 mg/m^2 on d 1, 8 every 21 days + Cisplatin 70 mg/m^2 on d 1 every 21 days	15	35	7	NR	44% at 1 year
Brewer et al.[19]	32	Gemcitabine 800 mg/m^2 on d 1, 8 every 28 days + Cisplatin 30 mg/m^2 on d 1, 8 every 28 days	0.0	21.9	37.5	3.5	NR
Dueñas-González et al.[20]	11	Gemcitabine 100 mg/m^2 once weekly + Cisplatin 33 mg/m^2 once weekly	0.0	36.3	36.3	NR	6 mo

[a] Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival; NR, not reported.
*Responders; #Non-responders.

on the Results of Treatment in Gynecological Cancer, 5-year survival for stages IB2, IIB, IIIB and IVA is 72.2, 63.7, 41.7 and 16.4%, respectively[21]. Over the last 20 years, concurrent chemoradiation trials have attempted to improve treatment results. Despite this, in 1996, a National Institutes of Health Consensus Statement on cervical cancer stated that there was no evidence that concurrent chemoradiation should be incorporated into standard practice[22]. Not until 1999 did five randomised studies involving nearly 2000 patients demonstrate that survival rates with concomitant radiotherapy and chemotherapy were superior to those obtained with radiation alone. Subsequently, two meta-analyses demonstrated that chemoradiation increased absolute survival by 10% and 13%, respectively[23,24]. More recently, a trial investigating cisplatin plus paclitaxel treatment with concurrent radiation therapy found that all of the 27 patients treated achieved a CR, although two patients experienced distant recurrence at 22 and 24 months after CR, and 1 patient had local progression 6 months after the end of radiotherapy[25].

Although chemoradiation therapy based on cisplatin is the standard treatment for locally advanced cervical carcinoma, the optimal scheduling and dosing have not yet been established. Evidence from the GOG-125 study indicates that weekly cisplatin (40 mg/m^2) for six cycles is equally effective and less toxic than cisplatin plus 5-fluorouracil in a 21-day schedule[26]. Importantly, these results obtained in the context of clinical trials with weekly cisplatin are reproducible in a clinical environment[27–29].

4.2. *Gemcitabine as a radiosensitiser*

Gemcitabine is a powerful radiosensitiser in cervical cancer cell lines, either alone or in combination with cisplatin[9,30,31]. As a single agent, McCormack et al. studied 10 previously untreated patients with stage IB2–IIIB cervical cancer. External beam radiotherapy (EBRT) consisted of 50.4 Gy given in 28 fractions over 5.5 weeks, plus high-dose-rate intracavitary brachytherapy. Gemcitabine was administered weekly for 6 weeks with dose escalation from 50 to 150 mg/m^2. No dose-limiting toxicities were found. All but one patient were disease-free at the median follow-up of 29 months (range 9–33 months), which strongly supports the preclinical data concerning its potent radiosensitising properties[32].

Pattaranutaporn et al. reported results of a phase II trial using gemcitabine (300 mg/m^2) weekly for 5 weeks during EBRT of 50 Gy in 2-Gy fractions in 19 FIGO stage IIIB patients. At this dose gemcitabine was well tolerated with no grade IV toxicities reported. All but two patients achieved a CR, and, at the median follow-up of 20 months, rates of disease-free and overall survival were 84% and 100%, respectively[33]. Boulaga et al. achieved similar results for efficacy and toxicity[34]. The high activity and tolerability of gemcitabine during radiation were also reported by Cetina et al. in patients suffering from renal dysfunction secondary to ureteral obstruction by the tumour[35].

Gemcitabine synergises with not only radiation but also cisplatin. Alvarez et al. used a twice-weekly regimen of cisplatin (30 mg/m^2) plus gemcitabine (20 mg/m^2) in 60 patients. Pelvic EBRT was delivered in 23 fractions over 5 weeks, for a total dose of 46 Gy. In addition, two brachytherapy insertions were made at weeks 3 and 5. This scheme proved toxic, so cisplatin was administered just once a week. At this level, grade III or IV haematological toxicities were maintained below 10%. At 51 months, the CR rate was 88.3% and the survival rate was 68.3%[36,37]. Zarba et al. reported a phase I/II study using fixed-dose cisplatin (40 mg/m^2) plus an escalating dose of gemcitabine starting at 75 mg/m^2 in 36 patients. Radiation consisted

Table 2 – Phase II studies of gemcitabine as a radiosensitiser alone or combined[a]

Authors [ref]	Schedule	No. of patients	CR (%)	DF/alive (%)
Pattarranutaporn et al.[33]	Gemcitabine 300 mg/m^2 (weekly)	19	89	8/100*
Boualga et al.[34]	Gemcitabine 300–600 mg/m^2 days 1, 8, 15, 40 and 47	19	74	NR/47
Cetina et al.[35]	Gemcitabine 300 mg/m^2 (weekly)	9	89	78/100#
Alvarez et al.[36,37]	CDDP 30 mg/m^2 gemcitabine 20 mg/m^2 (both twice-weekly)	60	88	NR/68.3‡
Zarba et al.[38]	CDDP 40 mg/m^2 + gemcitabine 125 mg/m^2 (both weekly)	36	89	81/NR§
Dueñas-González et al.[40]‖	CDDP 40 mg/m^2 (weekly) vs. CDDP 40 mg/m^2 + gemcitabine 125 mg/m^2 (both weekly)	40 43	Path 55 Path 77	NR/95 NR/100
Umanzor et al.[41]	CDDP 40 mg/m^2 + gemcitabine 125 mg/m^2 (both weekly)	20	90	80/100¶

[a] Abbreviations: CR, complete response; DF, disease-free; NR, not reported; CDDP, cisplatin.
*Median follow-up 20 months. #Median follow-up 11 months, trial in patients with renal failure. ‡After three patients CDDP was administered weekly. §Median follow-up 14 months. ‖Randomised study; patients underwent radical hysterectomy after external beam radiation therapy. ¶Median follow-up 12 months.

Table 3 – Ongoing phase III studies of gemcitabine as a radiosensitiser[a]

No. of patients	Treatment arms	Radiation
516	CDDP 40 mg/m^2 vs. CDDP 40 mg/m^2 + gemcitabine 125 mg/m^2 + two post-brachytherapy 21-day adjuvant courses CDDP 75 mg/m^2 d 1 plus gemcitabine 1 g/m^2 d 1, 8	EBRT 50.4 Gy + brachytherapy (both arms) (NCT00191100)
360	CDDP 40 mg/m^2 + gemcitabine 125 mg/m^2 vs. CDDP 40 mg/m^2 + gemcitabine 125 mg/m^2	EBRT 50 Gy in 2 Gy fractions + brachytherapy EBRT 50 Gy in 2 Gy fractions + radical hysterectomy

[a] Abbreviations: CDDP, cisplatin; EBRT, external beam radiation therapy.

of 50.4 Gy in fractionated doses over 5 weeks, followed by brachytherapy at 30–35 Gy delivered to point A. The recommended weekly dose of gemcitabine to be used with cisplatin was 125 mg/m^2. Grade III toxicity was mostly non-haematological. Similar to other studies with the combination, the CR rate in the 36 evaluable patients was 89%, and, at a median follow-up of 14 months, 81% were reported disease-free[38].

A phase II randomised study[39] compared the rate of pathological CR as a surrogate marker of survival between the experimental arm of cisplatin plus gemcitabine using Zarba's regimen (cisplatin [40 mg/m^2] plus gemcitabine [125 mg/m^2] versus cisplatin [40 mg/m^2] alone). A total of 83 patients staged as IB2, IIA and IIB were randomised to receive six weekly courses of one of the two schemes during EBRT, which consisted of 50 Gy in 2-Gy fractions. Within 3 weeks of radiation, patients underwent radical hysterectomy with pelvic and paraaortic lymphadenectomy. The results of this study are quite promising despite the combined regimen proving to be more toxic. Complete pathological response was 55% (95% confidence interval [CI]: 35.5–73) in the cisplatin group and 77.5% (95% CI: 57–90) for the gemcitabine plus cisplatin arm (P = 0.0201) (Table 2)[40].

These results led to a multicentre, open-label, phase III study in which 500 evaluable FIGO stage IIB–IVA patients were randomised to cisplatin (40 mg/m^2) and gemcitabine (125 mg/m^2) during EBRT, followed by brachytherapy plus two courses of adjuvant cisplatin plus gemcitabine, or to the control arm of cisplatin chemoradiation at 40 mg/m^2 with no adjuvant therapy. The study has closed and results are pending. Interestingly, the remarkable pathological response rate obtained with gemcitabine plus cisplatin and chemoradiation without brachytherapy has led authors to test whether brachytherapy is dispensable. Thus, in an ongoing phase III study for IB2–IIB patients, while both arms receive cisplatin plus gemcitabine concurrent to EBRT, they are randomised to either receive brachytherapy or radical hysterectomy (Table 3).

Recently, another phase I study of the gemcitabine plus cisplatin combination was reported where gemcitabine (100 mg/m^2 or 50 mg/m^2) was administered before cisplatin (40 mg/m^2)[42]. Radiation consisted of 45–50 Gy in 25 daily fractions combined with brachytherapy to deliver at least 85 Gy at point A. Surprisingly, the study was stopped due to dose-limiting toxicity even after halving the gemcitabine dose. All patients had a CR, which was pathologically confirmed in four. The authors concluded that, if gemcitabine is administered prior to cisplatin with radiation for cervical cancer, a reduction of cisplatin dose is likely to be required[42]. Determining whether the order in which gemcitabine and cisplatin are administered has an effect on patient outcome will require additional testing. The results of another study of cisplatin plus gemcitabine with Zarba's

Table 4 – Phase II studies of neoadjuvant chemotherapy with gemcitabine plus platinum therapy[a]

Authors [ref]	Treatment (chemotherapy)	No. of patients	Stage	Clinical response (%)	Pathological CR (%)
Dueñas-González et al.[46]	CDDP 100 mg/m^2 + gemcitabine 1000 mg/m^2, d 1, 8, every 21 days (3 cycles)	41	IB2–IIIB	ORR 95 Res. R. 56	23
Dueñas-González et al.[47]	Oxaliplatin 130 mg/m^2 + gemcitabine 1250 mg/m^2, d 1, 8, in a 21-day course (3 cycles)	10	IB2–IIIB	ORR 80 Res. R. 70	14
Termrungruanglert et al.[48]	CDDP 70 mg/m^2 + gemcitabine 1000 mg/m^2, d 1, 8, every 21 days (2 cycles)	18	IB2–IIA	ORR 84 Res. R. 89	6

[a] Abbreviations: CDDP, cisplatin; CR, complete response; ORR, overall response rate; Res. R., Resectability rate.

regimen (cisplatin first) report a CR rate of 90% (18 of the 20 patients evaluated) with moderate toxicity. At 12-month median follow-up, 80% (16 of the 20 patients) were disease free[41]. Together, these data clearly point to gemcitabine being a promising radiosensitiser in cervical cancer. The results of the multicentre randomised trial comparing cisplatin versus cisplatin plus gemcitabine are eagerly awaited.

4.3. *Neoadjuvant chemotherapy*

In the 1980s, several randomised trials tested neoadjuvant chemotherapy in locally advanced cervical cancer. Recent meta-analyses have supported previous conclusions that neoadjuvant therapy followed by radiation offers no significant benefit (hazard ratio [HR] = 1.01, 95% CI: 0.88–1.15, P = 0.913)[43]; however, a meta-analysis of trials comparing neoadjuvant chemotherapy followed by surgery with radiation alone showed a highly significant benefit, with a 36% reduction in the risk of death (HR = 0.64, 95% CI: 0.52–0.79, P = 0.00003), which is equivalent to an absolute improvement in survival of 15% (8–21%) at 5 years, increasing survival from 45% to 60%[44].

The meta-analysis results of this modality indirectly suggest that it is as effective as the current standard of cisplatin-based chemoradiation. However, the five studies included in the meta-analysis[44] used a chemotherapy based on cisplatin plus 'old' drugs such as vincristine and bleomycin, which are clearly not as effective as later drugs[45].

In addition, the ongoing European Organisation for Research and Treatment of Cancer (EORTC)-55994 study will compare the overall survival, PFS, toxicity and quality of life of patients treated with neoadjuvant cisplatin-based chemotherapy followed by radical hysterectomy versus standard therapy comprising concurrent radiotherapy and cisplatin-based chemotherapy.

4.4. *Gemcitabine as neoadjuvant therapy*

So far, three neoadjuvant trials using gemcitabine have been reported: two with cisplatin and another with oxaliplatin. In the first trial, 41 IB2–IIIB patients received three 21-day courses of cisplatin (100 mg/m^2) on day 1 and gemcitabine (1000 mg/m^2) on days 1 and 8, followed by locoregional treatment with either surgery or concomitant chemoradiation. The overall objective response rate was 95% (95% CI: 88–100%): three patients had a CR (7.5%) and 35 patients had a PR (87.5%). A complete pathological response was found in six (26%) of the 23 surgery patients and toxicity was mild[46].

A similar study using three cycles of oxaliplatin (130 mg/m^2) on day 1 and gemcitabine (1250 mg/m^2) on days 1 and 8 was completed in 10 patients with stage IB2–IIIB disease. The overall clinical response rate was 80%, producing a CR in three patients (30%) and a PR in five patients (50%). Seven (70%) patients underwent surgery. Haematological toxicity was moderate, with granulocytopenia grades III and IV observed in 23% and 3% of patients, respectively. At the median follow-up of 11 months (range 10–12 months), all patients were disease free[47]. A third study, performed in 28 patients (18 of which had bulky IB2 disease), used two cycles of cisplatin (70 mg/m^2) on day 1 of a 21-day cycle plus gemcitabine (1000 mg/m^2) on days 1 and 8, followed by radical surgery or radiation. On evaluation after induction chemotherapy, nine patients (33.3%) had a CR, 15 (55.5%) achieved a PR, and three (11.1%) had stable disease. The 24 patients who responded underwent surgery. Two of the nine CR patients had pathological CRs. Grade III or higher toxicities were limited to 13 cases[48]. Interestingly, a comparison between two similar patient cohorts, one treated with neoadjuvant cisplatin plus gemcitabine[46] and the other with standard cisplatin-based chemoradiation, reported no statistically significant differences in overall survival at median follow-up of 28 and 24 months, respectively (Table 4)[49].

These data suggest that these treatments could be equivalent. However, this requires confirmation, and currently the EORTC is performing a randomised comparison of these two treatment modalities.

5. Conclusions

The treatment of the early stages of cervical cancer still relies on local or radical surgical procedures to obtain a high cure rate. In metastatic and recurrent

disease, the most significant progress has been the demonstration that combination chemotherapy using a cisplatin plus topotecan regimen is superior to single-agent cisplatin. However, the optimal drug combination has yet to be determined. Among non-cisplatin drugs, gemcitabine has clearly shown activity and good tolerability. The results of the current GOG-204 trial should eventually confirm whether there is a role for cisplatin plus gemcitabine in treating metastatic and recurrent disease. Regarding the treatment of locally advanced disease, concurrent chemoradiation with cisplatin is the standard regimen. However, newer radiosensitisers should eventually improve treatment results. Among cytotoxic agents with radiosensitising properties, gemcitabine has demonstrated promising activity, both alone and in combination with cisplatin. A randomised phase II trial demonstrated the superiority of a cisplatin plus gemcitabine combination over cisplatin alone in terms of pathological CR rate, and an ongoing phase III trial will eventually confirm these results regarding survival. Finally, the merits of neoadjuvant chemotherapy followed by surgery for treating locally advanced disease are being studied. If it is eventually proven that neoadjuvant therapy is at least as good as cisplatin chemoradiation, the neoadjuvant combination of cisplatin plus gemcitabine should be considered.

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