A review of topotecan in combination chemotherapy for advanced cervical cancer

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Abstract: Treatment of advanced, recurrent or persistent cervical cancer includes radiotherapy and chemotherapy. Radiation has been the primary treatment modality for locoregionally advanced cervical cancer. Concomitant systemic cisplatin chemotherapy and radiation have shown high response rates with improvements in durable remissions and overall survival. Cisplatin has been the standard medication for the treatment of advanced cervical cancer. Combinations with other chemotherapeutic agents have been the subject of clinical trials with varying results. The toxicity of combination chemotherapy and tolerability of patients are other factors that should be considered in the management of patients with advanced disease. Recently topotecan, in combination with cisplatin, achieved increased response and overall survival rates without further compromising the patients' quality of life. This review focuses on the mechanism of action and toxicities of topotecan, as well as its role as a radio-sensitizer and chemotherapeutic agent in the management of advanced, recurrent, or persistent cervical cancer. Other combination modalities and dosages are also discussed.

Keywords: topotecan, combination chemotherapy, advanced cervical cancer

Introduction

Invasive carcinoma of the cervix is the second cause of death in women worldwide, with an estimated 510,000 newly diagnosed cases and 280,000 deaths each year (Salslow et al 2007). In developing countries, cervical cancer is often the most common cancer in women. The American Cancer Society (ACS) Cancer Facts and Figures (2007) reported that an estimated 11,150 cases of invasive cervical cancer will be diagnosed in the United States, and an estimated 3,670 women will die from this disease.

Although the incidence of cervical cancer has declined markedly since the introduction of screening tests, the overall mortality rates have not changed in the past 25 years (Fiorica 2003). The American Cancer Society Guideline for the Early Detection of Cervical Cancer was reviewed and updated in 2002; for the first time, those recommendations incorporated options including liquid-based cytology and human papilloma virus (HPV) DNA testing (Salslow et al 2007).

The prognosis of advanced cervical cancer is discouraging. Recurrent, persistent or advanced cervical cancer responds poorly to current treatment modalities. Five-year survival rates have been approximately 41%–51% and 8%–17% for patients with regional and distant disease, respectively (Tiersten et al 2004). Recent addition of chemotherapy to radiation treatment has increased overall survival for patients with regional disease to greater than 60% (Whitney et al 1999). Four randomized trials of chemo-radiation demonstrated positive results prompting a National Cancer Institute (NCI) clinical announcement for change in standard of care (Keys et al 1999; Morris et al 1999; Rose et al 1999; Peters et al 2000).

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At the present time, there is no effective treatment for metastatic disease and recurrences. Studies of cisplatin chemotherapy in cervical cancer demonstrate response rates of approximately 20%–30% with a median survival of 6–7 months. For recurrent or metastatic disease, chemotherapy is palliative. Complete responses are unusual and generally limited to patients with lung metastasis (Berek et al 2005). The high mortality rate, low response rate to available treatments and short survival mandates investigation into more effective therapies.

Various treatment protocols have been suggested to increase the survival of patients with cervical cancer. These protocols include radiotherapy and chemoradiation for locoregional disease, and single or combination chemotherapy for widely metastatic or recurrent cancer.

If recurrent disease presents in the central pelvis, then pelvic exenteration by experienced surgeons may yield five-year success rate of 32%–62% in the appropriate patients (DuPont et al 2006). Chemotherapy represents the best therapy for recurrent disease not curable by exenterative surgery. Chemotherapy is also the most reasonable option for patients presenting with distant metastases.

Topotecan is an effective chemotherapy agent for treatment of ovarian cancer and small-cell lung cancer. It was approved for use in combination with cisplatin by the US Food and Drug Administration (FDA) in 2006 for treatment of women with stage IVB, recurrent, or persistent carcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy (Brave et al 2006). This article will review the role of topotecan in the treatment of advanced (stage IV or widely metastatic) and recurrent cervical cancer.

Pharmacology of topotecan

Topotecan is a semisynthetic derivative of the pentacyclic alkaloid, camptothecin that is isolated from the Chinese yew tree, *Camptotheca acuminata*. The family of camptothecins includes irinotecan, topotecan, and 9-aminocaptothecin (Randall-Whitis et al 2007).

Two mechanisms of action have been described for topotecan. The principal mechanism is inhibition of DNA topoisomerase I. During normal DNA replication double stranded DNA separates and topoisomerase I regulates the broken DNA strand. This break is reversible and non-lethal for cell, but camptothecins convert this single stranded break to an irreversible double stranded break (Randall-Whitis et al 2007). This results in inhibition of RNA transcription and apoptotic cell death. Camptothecins exert their cytotoxic effect predominantly in cell in S phase because of their selective topoisomerase I poisoning effect (Ling et al 2001).

The second, recently discovered mechanism of action of topotecan is inhibition of the hypoxia-inducible factor (HIF). This mechanism is of particular interest in cervical cancer, because tumor tends to be either bulky or present in radiated fields, which often results in tumor hypoxia. HIF is a transcriptional factor, which induces expression of genes encoding proteins enabling cell survival in hypoxic condition. These proteins induce glycolytic enzymes required for anaerobic metabolism and growth factors such as vascular endothelial growth factor that stimulates tumor angiogenesis, as well as erythropoietin that increases the potential of oxygen delivery to the tumor (Belozerov VE. Van Meir EG. 2005).

Topotecan as a single agent in cervical cancer

Topotecan, in preclinical studies, demonstrated significant in vitro activity of solid tumor explants derived from colorectal, breast, ovarian, renal cell, non-small cell lung cancer, and gastrointestinal sources. Notable activity was also demonstrated in vivo in a wide range of animal tumor models.

Rowinsky et al (1997) reviewed phase 1 clinical studies with topotecan with as many as 14 different dosing schedules. Complete and partial responses were demonstrated in patients with a wide variety of solid tumors including squamous cell carcinoma. Myelosuppression was the major dose-limiting toxicity across all schedules, and non-hematologic toxicities were generally mild. Based on this information, there was substantial enthusiasm for further evaluating topotecan in a wide range of cancer patients in phase II studies.

Muderspach et al (2001) conducted a Gynecologic Oncology Group (GOG) phase II multicenter study (GOG 76-U) in patients with advanced, recurrent or persistent squamous cell carcinoma of the uterine cervix. Intravenous topotecan was administered at 1.5 mg/m^2 per day for 5 consecutive days every 4 weeks in patients without prior chemotherapy, aside from chemosensitizing agents used in conjunction with radiotherapy. The median progression-free interval was 2.4 months. The median overall survival was 6.4 months. The overall response rate (complete and partial) was 18.6%. Hematological toxicity was common, with 68% of patients experiencing grade 4 neutropenia and 18% grade 4 thrombocytopenia. Grade 3–4 gastrointestinal and neurologic toxicities were seen in 9% and 5% of patients. However, in patients with prior radiation and borderline renal function, dose reduction of 1.25 mg/m^2 is recommended. Topotecan

administered at this dose and schedule demonstrates moderate activity with substantial hematological toxicity.

Bookman et al (2000) reported on a multicenter phase II study of patients with previously treated squamous cell carcinoma of cervix (GOG 127-F) who had received one prior chemotherapy regimen . Patients received topotecan 1.5 mg/m^2 daily for 5 consecutive days on a 21-day cycle. The overall response rate was 12.5%. Progression free interval was 2.1 months and overall survival was 6.6 months. Topotecan had less gastrointestinal toxicity than irinotecan, another derivative of camptothecin with similar overall response rate. The single agent activity of topotecan in cervical carcinoma was also the subject of a report by Noda et al (1996) in which 4 of 22 (18%) evaluable patients achieved a partial tumor response.

Most clinical studies have used a 5-day regimen of short intravenous infusions. However, the optimal schedule has not yet been defined. Phase I/II studies have examined 24 hour infusions every 3 weeks versus continuous intravenous for 21 days. These data suggested that topotecan delivered as a continuous intravenous infusion over 21 days as a single-agent therapy does not appear to offer a clinical advantage over conventional 5-day schedules (Hochester et al 1994; Van Warmerdam et al 1995; Mainwaring et al 1997).

Topotecan in combination chemotherapy in cervical cancer: cisplatin and topotecan studies

Cisplatin represents the most active single agent in palliative chemotherapy-appropriate cervical cancer and single agent topotecan has demonstrated activity in treatment of cervical cancer. In previous clinical trials of platinum-based therapies in patients with widely metastatic or recurrent cervical cancer, there has often been a tradeoff between response rate and tolerability of treatment regimens, often with no differences in survival for the regimens with more severe toxicity profiles. GOG trial (GOG 110) compared cisplatin monotherapy with two cisplatin-based combination regimens (cisplatin/mitolactol and cisplatin/ifosfamide). Despite higher response rates for the combination therapies, no significant differences in survival were detected; moreover, the cisplatin/ifosfamide group suffered significant neurotoxicity (Omura et al 1997).

Cisplatin monotherapy has also been compared with cisplatin/paclitaxel in patients with recurrent or persistent cervical cancer (GOG Trial 169). The combination therapy was associated with a significantly increased response rate over cisplatin alone (36% vs 19%, p = 0.002) with no difference in median survival (9.7 vs 8.8 months). The cisplatin/paclitaxel group did experience higher incidence of grade 3–4 neutropenia (67% vs 3%) and anemia (27% vs 13%), and grade 1–4 neuropathy (36% vs 21%) (Moore et al 2004).

Topotecan and cisplatin have non-overlapping toxicities; therefore, a phase II trial of topotecan and cisplatin in persistent or recurrent squamous and non-squamous of the cervix was preformed. The tolerability of the cisplatin/topotecan combination has been established in phase I trials (Rowinsky et al 1997; Bell et al 2001; Dunton et al 2002). Based on dose-limiting hematological toxicities, the recommended doses for follow up in phase II studies were 0.75 to 1 mg/m^2/day of topotecan for 5 days and 50 mg/m^2 of cisplatin on day one.

A phase II trial of cisplatin and a 3-day topotecan regimen was studied with the hypothesis that this would be less bone marrow suppressive especially in previously irradiated patients. The overall response rate in this trial was 28% and median overall survival of 10 months and median progression-free interval of 5 months (Fiorica et al 2002). Importantly, in this trial responses were seen in tumor in previously irradiated fields.

Long et al (2005) in GOG-0179, a randomized phase III trial, demonstrated a survival advantage for combination chemotherapy over cisplatin alone in advanced cervical cancer. Their regimen included cisplatin 50 mg/m^2 q 21 days vs cisplatin 50 mg/m^2 day 1 + topotecan 0.75 mg/m^2 for 3 days q21 days vs a methotroxate, vinblastin, doxorubicin and cisplatin (MVAC) arm. The MVAC arm was closed due to 4 treatment-related deaths among 63 patients and was not included in the final analysis of the study.

Two hundred ninety-four patients enrolled onto the remaining regimens: 146 to cisplatin and 147 to cisplatin/topotecan. Grade 3 to 4 hematological toxicity was more common with cisplatin/topotecan (see Table 1, 2). Patients receiving cisplatin/topotecan had statistically superior outcomes to those receiving Cisplatin alone, with median overall survival (OS) of 9.4 and 6.5 months (p = 0.017), median progression free survival (PFS) of 4.6 and 2.9 months (p = 0.014) and response rate of 27% and 13%, respectively. This trial demonstrated improved PFS and OS when compared with single-agent therapy (Long et al 2005).

Topotecan plus cisplatin combination regimen was approved by the Food and Drug Administration (FDA) in 2006, for use in recurrent, or persistent carcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy. Brave et al (2006) reviewed the database supporting this approval.

Table 1 Hematologic adverse events in patients treated with topotecan + cisplatin or cisplatin alone (derived from data of Long et al 2005)

Adverse events	Grade	TC 140 patient	C 144 patient
Anemia	3	47 (34%)	28 (19%)
	4	9 (6%)	5 (3%)
Leukopenia	3	58 (41%)	1 (1%)
	4	35 (25%)	0 (0%)
Neutropenia	3	36 (26%)	1 (1%)
	4	67 (48%)	1 (1%)
Thrombocytopenia	3	36 (26%)	5 (3%)
	4	10 (2%)	0 (0%)

Abbreviations: C, cisplatin; TC, topotecan + cisplatin.

The GOG instituted a multi-arm trial of cisplatin in combination with vinorelbine, gemcitabine, paclitaxel or Topotecan (GOG-204). Earlier this year, the GOG interim analysis closed the study when data "indicated that all the experimental arms… were unlikely to demonstrate improved survival over control (cisplatin and paclitaxel)". Unfortunately, the toxicity data from the four arms will not be revealed until the survival data mature. Thus it is difficult to conclude if one arm is superior on the basis of toxicity given presumably similar survival rates. Based upon phase III data, Topotecan/cisplatin carries greater hematological toxicity but less risk of neuropathic pain. A guiding principle for palliative chemotherapy is minimization of symptoms and side-effects that worsens a patient's quality of life. In our institution, we favor the FDA approved combination until data from GOG-204 are published.

Other combinations of topotecan

A combination of topotecan and paclitaxel for treatment of persistent, recurrent or metastatic cervical cancer was investigated in a phase II study of 15 patients. The treatment protocol consisted of 175 mg/m^2 paclitaxel on day1 and 1 mg/m^2 topotecan on days 1–5 of a 25-day cycle with granulocyte colony stimulating factor (GCSF) support and the standard pretreatment regimen for paclitaxel. Overall response was 54% and progression-free survival 3.7 months with a median overall survival of 8.6 months. Grade 3/4 toxicities included anemia (47%), leukopenia (27%), neurotoxicity (13%), thrombocytopenia (13%), and diarrhea (13%) (Tiersten et al 2004).

Table 2 Non-hematologic adverse events in patients treated with TC or C alone (derived from data of Long et al 2005)

Adverse events	TC	C
Gastrointestinal	45%	28%
Pain	22%	16%
Metabolic-Laboratory	14%	10%
Hepatic	5%	1%
Dermatologic	48%	20%

Abbreviations: C, cisplatin; TC, topotecan + cisplatin.

The several combination chemotherapeutic protocols have not shown improved response, or had similar response with more severe toxicities in most patients than those treated by Cisplatin and topotecan combination (see Table 3).

Quality of life (QOL) during topotecan treatment

Several studies have investigated the QOL in patients with advanced cervical cancer with treatments. Patient-reported QOL measures are an important considerations when using chemotherapy with non-curative intent. Monk et al (2005) examined QOL data in conjunction with the GOG randomized phase III trial of cisplatin with or without topotecan. They demonstrated no statistically significant differences in QOL up to 9 months after randomization. QOL was assessed using Functional Assessment of Cancer Therapy-General (FACT-G), Cervix subscale (Cx subscle), FACT/GOG-Neurotoxicity subscale (NTX subscale), Brief Pain Inventory(BPI), and UNISCALE (UNI). They concluded that despite increased hematological toxicity, cisplatin/topotecan did not significantly reduce the QOL when compared with cisplatin alone ($p = 0.0016$).

Toptecan and radiation

Topotecan has also been examined as a radiosensitizing agent due to its ability to both sabotage repair of sublethal cell injury and to prevent HIF-regulated hypoxic cell survival. Dunton and coworkers (2002) studied the maximal tolerance dose (MTD) of topotecan with external beam radiotherapy in advanced cervical cancer. They concluded that topotecan can be safely administered at a dose of 1 mg/m^2 daily for 5 days on days 1–5 and 22–26 concomitantly with radiotherapy without significant toxicity. Grade III anemia in one case and grade II leukopenia in two cases were seen at this dose level. Dose limiting toxicity was not reached.

Bell and associates (2001) published a phase I study using topotecan during radiation implant after completion of external-beam therapy. He found the maximum tolerated dose of 0.5 mg/m^2. The data differed by dose and pretreatment with external beam therapy.

Future directions

Several phase II studies have demonstrated topotecan to be an active agent in cervical cancer. (Table 4)

Table 3 Combination regimens in treatment of persistent or recurrent cervical cancer

Author	Agent	Dose	Response Rate %	Toxicity
Brewer et al 2006	C+gemcitabine	30 mg/m^2+800 mg/m^2/d 1,8 Q 28 d	22	Hematologic
Mannel et al 2000	C+pentoxifylline	75 mg/m^2+1600 mg PO 9 d Q8H q21d	10	N/V 32%, hematologic 23%
Zanetta et al 1999	C+ifosfamide+paclitaxel (TIP)	75 mg/m^2+5 g/m^2+175 mg/m^2	52	Myelotoxicity 91%
Choi et al 2006	(TIP)	50 mg/m^2+1500 mg/m^2+135 mg/m^2	46.7	Neutropenia 13%- neurotoxicity 5%
Pohlmann et al 2002	C+decitabine	40 mg/m^2+50 mg/m^2 q21d	38.1	Neutropenia 68%
Maluf et al 2006	C+Tirapazamine	75 mg/m^2+330 mg/m^2	27.8	Anemia, fatigue, N/V
Serkies et al 2006	C+ifosfamide+mitomycin	50 mg/m^2+3 g/m^2 q21d	34	Leukopenia 59%
Muggia et al 2004	C+irinotecan	25 mg/m^2+65 mg/m^2 q21d	16	Myelosuppression+gastrointestinal
Ohwada et al 2004	Irinotecan+nedaplatin	50 mg/m^2/d 1,8,15+60 mg/m^2/d 1q4wk	40	Leukopenia 40%, neutropenia 38%

Abbreviations: C, cisplatin; TIP, cisplatin + ifosfamide + paclitaxel; N/V, nausea/vomiting

In an effort to ameliorate toxicity noted with 3- to 5-day dosing regimens of topotecan, investigators are currently recruiting patients in a phase I study for efficacy of weekly topotecan with cisplatin in advanced stage or recurrent cervical cancer. Topotecan will be given weekly at escalating dose levels starting at 2.0 mg/m^2 with standard cisplatin at 50 mg/m^2 every 21 days (available at www.clinicaltials.gov identifier NCT00322920). Also, a phase II evaluation of weekly topotecan is currently underway in patients with persistent or recurrent carcinoma of the cervix (available at http://ycctrials.med.yale.edu/listprotocolsbydisease.asp).

Weekly topotecan in combination with pemetrexed is in a phase I trial in patients with advanced malignancies (available at www.clinicaltials.gov Identifier NCT00315861).

Lastly, the combination of paclitaxel together with topotecan and cisplatin in treating patients with advanced, persistent, or recurrent cervical cancer is being evaluated in a phase II trial (available at www.clinicaltrials.gov ID numbers CDR000456248; GOG-0076EE).

In an effort to further improve radiosensitization, phase II trials is currently underway studying topotecan and cisplatin with radiation in cervical carcinoma (available at www.clinicaltrials.gov Identifier NCT00257816; NCT003220983 and NCT000287911). It is expected that synergy between the drugs due to downregulation of HIF by Topotecan in poorly perfused tumors.

Conclusion

Improvements in cervical cancer screening have led to a decline in the incidence of cervical cancer, but this diseaese is still a leading cause of cancer related mortality worldwide. Advances in the treatment of cervical cancer have led to the use of chemoradiation in locally advanced disease, but few treatment options remain for women with advanced, recurrent, or persistent disease. Topotecan and cisplatin combination approved by FDA have produced higher survival and progression free survival rates in the management of these patients. Data from GOG 204 will need to be evaluated to determine the effect of survival with combination therapy. Topotecan is being investigated in its role as a chemosensitizer in patients receiving radiotherapy. Ongoing studies to find better combination and dosing regimen with less toxicity and more efficient therapy are needed to continue

Table 4 Topotecan in phase II studies for treatment of recurrent cervical carcinoma

Study	Treatment history	Treatment	Number of patients	PFS	RR	OS
Noda et al 1996	76% prior chemotherapy	Topotecan 1.2 mg/m^2, 5 days	22	NR	18%	NR
Abu-Rustam et al 2000	Platinum prior based chemotherapy	Topotecan 1 mg/m^2/d on days 1–5 of a 21-day cycwle	12	NR	17%	NR
Muderspach et al 2001	No chemotherapy	Topotecan 1.5 mg/m^2	40	2.1	13%	6.4
Bookman et al 2000	88% prior chemotherapy	Topotecan 1.5 mg/m^2	40	2.1	13%	6.6
Fiorica et al 2002	No chemotherapy	Topotecan 0.75 mg/m^2 + cisplatin 50 mg/m^2	32	5	28%	10
Tiersten et al 2004	Prior radiotherapy	Topotecan 1 mg/m^2 + paclitaxel 175 mg/m^2	15	3.7	54%	8.62

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate.

to improve the QOL and survival of patients with persistent or recurrent cervical cancer.

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