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The role of cisplatin alternative regimens with radiotherapy in cervical cancer

In 1983, a double blind randomized control trial (RCT) demonstrated the benefit of radiosensitization with chemotherapy during radiotherapy on advance stage cervical cancer Piver et al., 1983. Sixteen years and approximately 127,600 cases of cervical cancer in the United States later, four RCTs showed chemotherapy to be the preferred option as a radiosensitizer concurrently with radiotherapy for advance cervical cancer (Keys et al., 1999; Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999). In the same year, the National Cancer Institute (NCI) made a clinical announcement stating that "strong consideration should be given to adding concurrent chemotherapy to radiation therapy in the treatment of invasive cervical cancer." However it remained to be determined whether single agent cisplatin was the optimal choice (National Cancer Institute, 1999). In fact, according to the NCI, "It is not possible from these trials to conclude which cisplatin-based regimen is the optimal one."

Over the past decade, several RCTs were conducted comparing cisplatin-based polychemotherapy versus cisplatin-only with radiotherapy. Petrelli et al. recently published a meta-analysis comparing standard concurrent weekly cisplatin and pelvic irradiation with other platinum containing regimens (Petrelli et al., 2014). Four prospective randomized trials and four retrospective studies were eligible, including approximately 1500 cervical cancer patients ranging from stage I to IVA. The authors concluded that platinum-based doublet therapy with concurrent irradiation is the "preferred treatment" and "potentially the best regimen" for stage IB-IVA cervical cancer, with enhanced locoregional control and minimally increased toxicity compared to the traditional single agent weekly cisplatin. They even concluded that there was a suggestion of improved progression free and overall survival for doublet therapy.

The result of this meta-analysis shed a light on how standard treatment for advance stage cervical cancer can be improved by adding other chemotherapies to single agent cisplatin regimens. However, the authors did admit that there are limitations to their study and in those included in the meta-analysis. For instance, when looking closer at the four RCTs, two trials (Duenas-Gonzalez et al., 2005; Pu et al., 2013) included early and advance stage cervical cancer patients. The heterogeneity among the populations studied, limits the application of the study results to any specific subpopulations. The meta-analysis observed an increase in gastrointestinal toxicities, thrombocytopenia, and neutropenia as expected with the usage of cisplatin doublets, but concluded that toxicity is "minimally increased". This was also seen according to a RCT published by Roy et al. (2011). In this study however, the cisplatin gemcitabine doublet was much more dose intense comparing to the weekly cisplatin group. Despite an unequal dose intensity, and even though 60% of the doublet group could not complete therapy on schedule, the doublet outcomes were sufficiently favorable to suggest further studies of doublet therapy.

Aside from adding another agent to the weekly cisplatin chemotherapy, two additional RCTs from Ryu et al. and Nagy et al. also showed that weekly cisplatin is not the only choice for advance stage cervical cancer. Ryu et al. demonstrated that triweekly cisplatin 75 mg/m^2 every 21 days, concurrent with radiotherapy is more effective with an increase in overall 5 year survival of 18%, and a reduction in the risk of death by 62.5% (HR 0.375, $p = 0.03$). It was also overall less toxic than weekly cisplatin treatment. For instance, grade 3–4 neutropenia was approximately half of that seen with the weekly regimen (Ryu et al., 2011).

The results of Nagy et al. were similar, showing that daily cisplatin, 20 mg/m^2 for 5 days every three weeks has a superior five-year local relapse-free survival ($p < 0.01$), lesser toxicity, and a similar 5-year survival rate compared with the standard weekly cisplatin treatment (Nagy et al., 2012).

Based on the meta-analysis of Petrelli et al. and the 8 RCTs comparing single agent weekly cisplatin to other regimens (see Table 1), it is reasonable to conclude that weekly cisplatin is no longer the only option for chemosensitization with radiotherapy for locally advanced cervical cancer. We hope that a more comprehensive meta-analysis in the future will include some of these other trials that show a trend toward benefit for alternatives to weekly platinum. For instance, Pu et al. showed an intriguing trend toward improved 5 year local recurrence (79.3% versus 69.3%, $p = 0.061$) and overall survival (82.8% versus 74.3%, $p = 0.098$) Pu et al., 2013. It is likely that had a one tail test been used, the results would have been statistically significant. These slightly under powered studies are ideally suited for inclusion in meta-analyses.

Over more than 30 years, chemosensitization for cervical cancer has seen little change. The time between an early report of benefit (circa 1984) to widespread adoption (1999) of chemosensitization, may have cost the lives of many women who could have benefited from the improvement in overall survival. We are again at a pivotal time when alternatives to a comfortable standard are being challenged. Given the widespread large number of cases of new cervical cancer in the world today, any delay in adopting new advances may be costly.

Further studies are warranted to determine the optimal doublet or other alternatives to single agent weekly cisplatin. Further studies are not needed to justify continued use of single agent cisplatin. Let's not relive 1984.

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Table 1
Eight randomized control trial comparing polychemotherapy and weekly cisplatinadjunct to pelvic radiotherapy.

Author, year	Patient no. experimental/control arms	Stage	Median follow-up (months)	Chemotherapy schedules experimental/control arms	CT completion experimental/control arms	Surgery included as part of treatment plan	Outcomes (experimental/control arms)	
							Disease status	OS
Rose, 2007 (long term follow-up of 1999 study)	173	IIB–IVB	106	50 mg/m^2 CDDP IV on D1,D29 + 4 g/m^2 5-FU ci 96 hrs on D1,D29 + 2 g HU PO twice weekly at wks 1–6	CDDP 80.9%, 5-FU 79.2%, HU 19.7%	Nil	PFS: 43% at 10	53% at 10
	176			Conventional CDDP	49.4%		PFS: 46% at 10	53% at 10
Duenas-Gonzalez, 2011	43	IB2–IIB	20	6wk-40 mg CDDP + 125 mg Gem	63%	100%	CR pathologic[a]. 77.5%	p = 0.0201
	40			Conventional CDDP	82%		CR pathologic: 55%	
Kim, 2008	78	IIB–IVA	39	20 mg/m^2/d CDDP + 1000 mg/m2/d 5FU ci x 5 days, q28d x3 cycles	65%	Nil	PFS: 67% at 4	70% at 4
	77			6wk-30 mg CDDP	73%		PFS 66% at 4	67% at 4
Duenas-Gonzalez, 2011	259	IIB-IVA	46.9	6wk-40 mg CDDP + 125 mg Gem, with adjuvant 50 mg CDDP (D1) +1000 mg Gem (D1,8) x2 cycles	Median: 5 cycles Adjuvant: 76.5%	Nil	PFS:74.4% at 3 HR = 0.68 (95% CI, 0.49-0.95)	N/A HR = 0.68 (95% CI, 0.49–0.95),
	256			Conventional CDDP	Median: 6 cycles		PFS:65.0% at 3 p = 0.029	69.1% at 3 *p* = 0.0224
Ryu, 2011	53	IIB–IVA	60	Triweekly 75 mg CDDP x3 cycles	92.5%	Nil	5 recurrence rate: 24.5%	88.7% at 5 HR 0.375 (95% CI, 0.154–0.914)
	51			Conventional CDDP	86.3%		5 recurrence rate: 29.4%	66.5% at 5 *p* = 0.03
Nagy, 2012	164	IIB–IIIB	68.1	20 mg/m^2/d CDDP x5 days, q21d x2 cycles	Op: 78% non-op: 80%	59%	DFS: 73% at 5 p = 0.09	78% at 5 *p* = 0.14
	162			Conventional CDDP	Op: 83% non-op: 42%	67%	DFS: 69% at 5	72% at 5
Pu,2013	145	IB–IIA	60	5wk-30 mg CDDP + 30 mg DOC	79.3%	100%	RFS:79.3% at 5 HR 0.64 (95 % CI, 0.40-1.03)	82.8% at 5 HR 0.65 (95 % CI, 0.39–1.09) p = 0.098
	140			Conventional CDDP	75%		RFS:69.3% at 5 p = 0.061	74.3% at 5
Roy,2014	25	IIB–IIIB	17	6wk-40 mg CDDP +125 mg Gem	"10 patients completed within 10 wks."	Nil	DFS: 83% at 21 mos p = 0.69	100% at 21 mos p = 0.14
	25		21	Conventional CDDP	"most completed within 9 wks"		DFS: 73% at 21 mos	84.5% at 21 mos

5-FU: 5-fluorouracil; 6wk-40 mg CDDP + 125 mg Gem: 6 course of weekly 40 mg/m^2 cisplatin with 125 mg/m^2 gemcitabine; BT: brachytherapy; CDDP: cisplatin; ci: continue infusion; Conventional CDDP: 5–6 course of weekly cisplatin at 40 mg/m^2; CR pathologic: complete pathologic response rate; CT: chemotherapy; D1,D8: day 1, day 8; DFS: disease free survival; Gem: gemcitabine; HDR: high dose rate; HU: hydroxyurea; IV: intravenous; mos: months; N/A: not applicable; Op: operation; OS: overall survival; PFS: progression free survival; PO: orally; q28d: every 28 days; RFS: recurrence free survival; wks: weeks; DOC: docetaxel; yr: year.

[a] Those with no evidence of tumor cells or residual microscopic disease in the absence of any or intermediate- or high-risk factors for recurrence (near-complete).