Pharmacoeconomics of Cisplatin-Based Chemoradiation in Cervical Cancer: A Review

Peter G. Rose, MD, and Panos T. Lappas

ABSTRACT

Is the use of cisplatin-based chemoradiation therapy, which has become the new standard of care for locally advanced cervical cancer, cost-effective? To evaluate this, we conducted a pharmacoeconomic analysis of five recent phase III trials of cisplatin-based chemoradiation for the treatment of locally advanced cervical cancer. Using an economic model, we applied cost data figures to resource utilization data derived from the cisplatin-based chemoradiation arms of the five randomized trials. We examined the cisplatin-based chemoradiation benefits in terms of increased median survival time. Incremental costs were divided by the difference in survival to determine the cost per patient benefited. Costs per year of life gained were calculated based on both published survival and estimated survival rates. Costs of cisplatin-based chemoradiation regimens per year of life gained varied from $2,384 to $28,770 based on published survival and from $308 to $3,712 based on estimated survival rates. Variations in regimen cost were largely dependent on inpatient or outpatient administration. Inpatient administration costs for cisplatin and 5-fluorouracil were $8,339 per patient vs $3,590 per outpatient. Cisplatin-based chemoradiation regimens increased mean survival at an acceptable cost per year of life gained in both inpatient and outpatient settings.

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INTRODUCTION

Cervical cancer is a tremendous health problem worldwide where it remains the third most frequent cancer.[1] In regions where screening is not widely used, including Africa, Asia, and South America, it is the most frequent cancer among women. Even in the United States, despite improvements in screening utilization, certain populations, including Asian, Hispanic, African-American, American-Indian, and Appalachian white women are at high risk for cervical cancer.[2] The disease affects women at a younger age than other malignancies, and therefore improvements in cure profoundly affect longevity.[3]

The prognosis for cervical cancer depends on the stage at diagnosis, which is quite variable and related to the utilization of cervical cancer screening programs. In the US, approximately 4,100 patients annually are diagnosed with stage IIB-IVA disease and are candidates for radiation therapy with curative intent.[3] Additionally, 840 have stage IB2 or are found to have nodal metastasis during radical hysterectomy and may also receive radiation therapy.[3] Recently, five randomized trials comparing cisplatin-based chemoradiation to radiation alone or radiation with hydroxyurea have been performed in this patient population.[4-8]

Based on the results of these five trials, the National Cancer Institute released a "Clinical Alert" declaring use of chemotherapy concurrently with radiation therapy the new standard of therapy for patients with advanced cervical cancer.[9] The incremental costs that may be associated with chemoradiation, which have only recently been addressed, will be reviewed here.[10] Interest in these data may be greatest in countries with a high incidence of the disease, which also may have limited health care resources.

In the US, the growth of managed care and interest in research-based economic evaluations led us to analyze the economic impact of these five trials.[10] We compared the clinical results of cisplatin-based chemoradiation with the control arms of these trials, offering radiation alone or radiation with hydroxyurea, in terms of incremental cost per year of life gained (IC/YLG). Similar analyses were performed when paclitaxel and cisplatin were introduced as new standard therapies for ovarian cancer.[11-13] Health care economists and ethicists consider IC/YLGs of $40,000, $50,000, and

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Cisplatin-based chemoradiation demonstrates improved survival at an acceptable cost per year of life gained.

Although no randomized study exists, it appears that with the cisplatin and fluorouracil infusion, a cisplatin dose of 50 mg/m^2 is more cost-effective than 70 mg/m^2.

For regimens given in the inpatient setting in this study, chemotherapy administration costs account for more than 75% of the total incremental cost of chemoradiation therapy over radiation therapy alone.

Cisplatin-based chemoradiation regimens increased mean survival at an acceptable cost per year of life gained in both inpatient and outpatient settings.

Dr. Rose is director of gynecologic oncology and professor of reproductive biology and oncology in the Division of Gynecologic Oncology in the Department of Obstetrics and Gynecology at University Hospitals of Cleveland, Case Western Reserve University, in Cleveland, OH, and Mr. Lappas is manager, healthcare economics, at Bristol-Myers Squibb Oncology/Immunology in Princeton, NJ.

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TABLE 1. CISPLATIN-BASED CHEMORADIATION REGIMENS IN CLINICAL TRIALS ANALYZED

GOG 85
Cisplatin 50 mg/m² day 1 and 29 followed by 5-fluorouracil 1 g/m²/d as a 96-hour infusion day 1 and 29

RTOG 9001
Cisplatin 75 mg/m² day 1 and 29 followed by 5-fluorouracil 1 g/m²/d as a 96-hour infusion day 1 and 29

GOG 120
Either cisplatin 40 mg/m² day 1, 8, 15, 22, 29, and 35, or cisplatin 50 mg/m2 day 1and 29 followed by 5-fluorouracil 1 g/m2/d as a 96-hour infusion day 1 and 29 hydroxyurea orally 2 g/m² twice weekly

GOG 123
Cisplatin 40 mg/m² day 1, 8, 15, 22, 29, and 35

SWOG 8797/GOG 109
Cisplatin 70 mg/m² day 1, 29, 50, and 71 followed by 5-fluorouracil 1 g/m²/d as a 96-hr infusion day 1, 29, 50, and 71

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$75,000 or more acceptable for more costly new therapies.[14]

METHODS

The healthcare resources utilized for cisplatin chemo-radiation in each of the five trials were compared with those of the control arm (ie, radiation alone or radiation plus hydroxyurea). Radiation was considered standardtherapy prior to these trials and the radiation therapy was identical in each trial.[15] The economic evaluation was intended to capture incremental treatment costs; therefore, the costs of radiation were not included in the analysis. The healthcare resources used in our model were grouped into six categories: (1) drug acquisition, (2) concomitant medications, (3) laboratory procedures, (4) inpatient and outpatient treatment administration, (5) physician visits, and (6) adverse event management. Indirect treatment costs to the patient were not available for this analysis.

Published reports from the five randomized clinical trials were used to model the treatment algorithm for the chemotherapy portion of each trial, including duration of treatment. To ensure that treatment algorithms reflected actual healthcare utilization characteristics for each trial, physician input was used to validate the final models. The most commonly prescribed treatment setting (inpatient or outpatient) was used in each of the five models, although some physicians may choose to treat in an alternative setting in practice. Table 1 lists the cisplatin-based chemotherapy regimens and schedules from each of the five randomized clinical trials.

Adverse event grades and corresponding incidence rates for each treatment arm were gathered from the published trial reports. Typical treatment and resource utilization profiles were created for each adverse event grade through modeling, supplemented by physician input for validation purposes. Adverse event treatment profiles include professional services (physician and nursing fees), medications, and facility fee components. In the inpatient setting, diagnosis related groups (DRGs) that captured all resources used during management of the event were assigned.

This economic analysis was conducted from the perspective of the healthcare payor. Financial data used to populate the resource utilization models were obtained from a variety of publicly available data sources. Acquisition costs for chemotherapy and concomitant medications were based on data from the Drug Topics Red Book.[16] Laboratory tests, physician visits, and outpatient chemotherapy administration costs were gathered from the American Medical Association's Resource-Based Relative Value Scale (RBRVS) Physician's Guide.[17] Inpatient chemotherapy administration and adverse event management costs were determined using Medicare Provider Analysis and Review (MEDPAR) DRG reimbursement values, available online.[18] Since treatment did not extend beyond 1 year, it was not necessary to discount any of the financial data included in the analysis.

Overall costs for resources consumed during chemotherapy were calculated by summing costs per cycle of therapy and multiplying by number of cycles of therapy administered. Available patient outcome data was used to produce the cost-effectiveness analysis, including incremental survival rate and median survival to date. Total incremental costs associated with cisplatin-based chemotherapy were divided by the incremental survival to date to determine the incremental cost per patient benefited. Incremental cost per year of life gained (IC/YLG) to date was

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TABLE 2. RESOURCE UTILIZATION FOR CISPLATIN-BASED REGIMEN

Agent	Dose/Day (mg)*	Unit Size (mg)	Units/Day (n)	Days/Cycle (n)	Cycles/Therapy (n)	Cost/Unit	Cost/Therapy
Cisplatin 40 mg/m2 weekly, 6 weeks	68	50	2	1	5.5	$160.80	$1,768.77
Potassium	100	100	1	2	5.5	$0.36	$3.96
Magnesium	250	250	1	2	5.5	$0.02	$0.22
D5W/NSS	750 mL	250 mL	3	1	5.5	$9.30	$153.48
Ondansetron	8	4	2	2	5.5	$10.66	$234.57
Prochlorperazine	10	5	2	2	5.5	$0.57	$12.58

Outpatient administration	Code	Units/ Day (n)	Days/ Cycle (n)	Cycles/ Therapy (n)	Cost/Unit	Cost/Therapy
Outpatient visit	99212-5	1	1	5.5	$55.02	$302.62
Infusion (first hour)	96410	1	1	5.5	$57.23	$314.77
Hydration	90781	6	1	5.5	$20.91	$690.03

Tests	Units/Day (n)	Days/Cycle (n)	Cycles/Therapy (n)	Cost/Unit	Cost/Therapy
Chem 23	1	1	5.5	$16.00	$88.00
Magnesium	1	1	5.5	$3.84	$21.12

*Average body surface area=1.7m².

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TABLE 3. HEALTHCARE RESOURCES FOR CISPLATIN-BASED CHEMORADIATION

	GOG 85	GOG 120 (Weekly cisplatin)	GOG 120 (3-drug regimen)	RTOG 9001	GOG 123	SWOG 8797 (GOG 109)
Median patient age (years)	48	48	48	47	41	48
Chemotherapy agents	$689	$1,769	$1,142	$1,011	$1,930	$2,023
Concomitant medications	$147	$405	$147	$147	$442	$294
Laboratory tests	$40	$109	$40	$40	$119	$79
Physician costs	$719	$303	$719	$719	$330	$1,438
Inpatient administration	$8,120	n/a	$8,120	$8,120	n/a	$16,241
Outpatient administration	n/a	$1,005	n/a	n/a	$1,096	n/a
Adverse event management	$708	$777	$1,554	$708	$477	$708
Incremental cost (vs comparative therapy from trial)	$9,620	$2,575	$9,929	$10,676	$4,325	$20,714
Incremental survival rate*	0.11	0.27	0.25	0.15	0.16	0.18
Incremental cost/ patient-benefited	$87,455	$9,537	$39,716	$71,173	$27,031	$115,078
Median survival* (years)	6	4	4	5	4	4
IC/ YLG (published survival)	$14,576	$2,384	$9,929	$14,235	$6,758	$28,770
IC/YLG (estimated survival) to date	$2,821	$308	$1,281	$2,224	$711	$3,712

*Average body surface area=1.7m².

IC/YLG=incremental cost/year of life gained.

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computed by dividing the incremental cost per patient benefited by the current published survival. Since survival curves have plateaued in each of the five trials, it is possible to determine the IC/YLG based on estimated survival. This was determined by dividing the incremental cost per patient benefited by the difference between estimated longevity and the median age of enrollees in each trial.[19]

RESULTS

A sample of drug acquisition, concomitant medication, chemotherapy administration, physician visit, laboratory tests, and adverse event management costs for cisplatin-based chemotherapy is presented in Table 2. The costs of the chemotherapy regimens used in the five trials are presented in Table 3. The data reveal that, for regimens given in the inpatient setting, chemotherapy administration costs are the most significant components of treatment, accounting for more than 75% of the total incremental cost of chemoradiation therapy over radiation therapy alone. Drug acquisition cost for these regimens accounted for less than 12% of total incremental costs. For regimens administered in the outpatient setting, drug acquisition cost is most significant, accounting for 40% or more of the total incremental cost with chemoradiation.

For cisplatin-based chemoradiation, the IC/YLG varied from $2,384 to $28,770 based on published survival and from $308 to $3,712 based on estimated survival. These variations were largely dependent on treatment setting. The IC/YLG based on published survival ranged from $2,384 to $6,758 in the outpatient setting and from $9,929 to $28,770 in the inpatient setting. Based on estimated survival, IC/YLG ranged from $308 to $711 in the outpatient setting and from $1,281 to $3,712 in the inpatient setting.

In view of the potential savings afforded by the outpatient administration of cisplatin and fluorouracil, we calculated the costs of administering this regimen in the outpatient setting. We included administration costs of cisplatin (infusion, hydration, and physician visits) followed by home infusion of fluorouracil, which requires a PIC line insertion as well as a portable infusion pump. The results showed that costs of outpatient administration of this cisplatin and fluorouracil regimen were approximately 40% that of inpatient administration ($3,590 outpatient vs $8,839 inpatient).

TABLE 4. INCREMENTAL COST PER YEAR LIFE GAINED OF COMMON HEALTHCARE INTERVENTIONS

	IC/YLG
Colorectal cancer screening for people age 40+	$4,500
Center dialysis for end-stage renal disease	$55,000
Annual cervical cancer screening for women age 40+	$82,000
Colonoscopy for colorectal cancer screening for people age 40+	$90,000
Annual mammography for women age 55 to 64	$110,000
Bone marrow transplant and chemotherapy for breast cancer	$130,000
Multivessel coronary artery bypass surgery	$220,000

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DISCUSSION

This pharmacoeconomic evaluation of cisplatin-based chemoradiation in cervical cancer treatment suggests that the IC/YLG ratio with this therapy based on published survival will not exceed $30,000. Based on estimated survival, it will not exceed $4,000. To put the IC/YLG ratio into perspective, we sought similar ratios for other healthcare interventions. Table 4 depicts cost-effectiveness ratios for several common healthcare interventions obtained from the literature.[18] The ratios represent the IC/YLG with each intervention, and they range from less than $5,000 to more than $200,000 per year of life gained.

As noted, IC/YLG ratios of $40,000 to $75,000 or more have been considered acceptable for the introduction of more costly new therapies by healthcare economists and ethicists.[14] Cisplatin-based chemoradiation IC/LYG ratios fall well below this benchmark, indicating a favorable pharmacoeconomic profile for chemoradiation vs radiation alone in cervical cancer treatment.

Costs for inpatient administration of chemotherapy were substantially greater (3.8- to 9-fold) than outpatient administration in the five trials. Costs for outpatient administration of cisplatin and fluorouracil were substantially less but still 2.4-fold more expensive than weekly outpatient cisplatin therapy. Additionally, many cervical cancer patients or their families are not able to give home infusion. Since the relative risk of death using cisplatin chemoradiation in each of the trials was similar, the cost findings have significant implications. We discovered that with the cisplatin and fluorouracil infusion, a cisplatin dose of 50 mg/m^2 is more cost-effective than 70 mg/m^2. Additionally, continuation of chemotherapy beyond the completion of radiotherapy, as seen in SWOG trial 8797

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(GOG 109), substantially increases overall treatment costs. However, this trial, which was recently published, demonstrated an improved outcome for patients who completed 3–4 vs 1–2 cycles of therapy. Therefore, while there may be other factors such as patient compliance and performance status to consider, the increased cost may prove to be justified.

"...with the cisplatin and fluorouracil infusion, a cisplatin dose of 50 mg/m^2 is more cost-effective than 70 mg/m^2."

This modeling analysis provides a good representation of direct treatment costs and pharmacoeconomic outcomes associated with chemoradiation. Chemotherapy is, of course, associated with significant indirect costs as well. These can include time off from work due to chemotherapy administration and associated toxicities, transportation to and from the treatment site, and even resources donated by friends and family to aid in the patient's treatment. Although the magnitude of these indirect costs can be significant (and variable), they were not included in this study since we intended to capture only direct treatment costs. Survival data are still being updated; therefore, future looks at this economic analysis are warranted. The next step in evaluating the economic impact of chemoradiation in cervical cancer is to conduct a retrospective analysis at a specific site of care that will capture actual patient resource utilization, and further enhance this modeling study's validity and accuracy.

In summary, cisplatin-based chemoradiation administered in either the inpatient or outpatient setting adds a substantial benefit at an acceptable cost.

REFERENCES

1. 1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide frequency of eighteen major cancers in 1985. *Int J Cancer.* 1993;54:594-606.
2. Hampton JW. The disproportionately lower cancer survival rate with increased incidence and mortality in minorities and underserved Americans. *Cancer.* 1998;83:1687-1690.
3. *SEER Cancer Incidence Public Use Data Base, 1973-1994.* Bethesda, MD: National Cancer Institute; 1997.
4. Whitney CW, Sause W, Bundy BN, et al. A randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes. A Gynecologic Oncology Group and Southwest Oncology Group Study. *J Clin Oncol.* 1999;17:1339-1348.
5. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy versus pelvic and para-aortic radiation for high risk cervical cancer: a randomized Radiation Therapy Oncology Group clinical trial. *N Engl J Med.* 1999;340:1137-1143.
6. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based chemoradiation improves progression free and overall survival in advanced cervical cancer: results of a randomized Gynecologic Oncology Group study. *N Engl J Med.* 1999;340:1144-1153.
7. Peters WA III, Liu PY, Barrett RJ, et al. Cisplatin and 5-fluorouracil plus radiation therapy are superior to radiation therapy as adjunctive in high-risk early stage carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: report of a phase III intergroup study. *J Clin Oncol.* 2000;18:1606-1613.
8. Keys HM, Bundy BM, Stehman FB, et al. A comparison of weekly cisplatin during radiation therapy versus irradiation alone each followed by adjuvant hysterectomy in bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *N Engl J Med.* 1999;340:1154-1161.
9. NCI Clinical Announcement. Concurrent chemoradiation for cervical cancer. US Department of Public Health, February 1999.
10. Rose PG, Lappas PT. Analysis of the cost effectiveness of concurrent cisplatin-based chemoradiation in cervical cancer: implications from five randomized trials *Gynecol Oncol.* 2000;78:3-6.
11. Elit LM, Gafni A, Levine MN. Economic and policy implications of adopting paclitaxel as first-line therapy for advanced ovarian cancer: an Ontario perspective. *J Clin Oncol.* 1997;15:632-639.
12. McGuire W, Neuget AI, Arkian S, Doyle J, Dezii CM. Analysis of the cost-effectiveness of paclitaxel as alternative combination therapy for advanced ovarian cancer. *J Clin Oncol.* 1997;15:640-645.
13. Walker H, Stuart G, Bacon M, et al. Comparative cost-effectiveness of paclitaxel-cisplatin (TP) vs cyclophosphamide-cisplatin (CP) in women with advanced epithelial ovarian cancer: results from a randomized trial. *Proc Am Soc Clin Oncol.* 2000;19:379a.
14. Smith TJ, Hillner BE, Neighbors DM, McSorley PA, LeChevalier T. Economic evaluation of a randomized clinical trial comparing vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin for non-small-cell lung cancer. *J Clin Oncol.* 1995;13:2166-2173.
15. NIH consensus statement: cervical cancer. 1996;14:15-16.
16. *Drug Topics Red Book.* Montvale, NJ: Medical Economics Company, 1998.
17. *Medicare Resource-Based Relative Value Scale (RBRVS): The Physician's Guide.* Chicago, IL: American Medical Association; 1998.
18. *Medicare Provider Analysis and Review (MEDPAR).* Available at: http://www.hcfa.gov
19. National Canter for Health Statistics.
20. Tengs TO, Adams ME, Pliskin JS, et al. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal.* 1995;15(3):369-390.