Protocol Development for Ovarian Cancer Treatment in Kenya

A Brief Report

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Introduction: Ovarian cancer is a leading cause of cancer death for Kenyan women. Most women are diagnosed with an advanced stage of disease. The current North American standard of care includes surgery followed by carboplatin and paclitaxel. Neither drug is available for Kenyan women. We performed a literature search investigating chemotherapy in low-resource countries with the aim to write an evidence-based chemotherapy protocol for women diagnosed with ovarian cancer in Eldoret, Kenya, at the Moi Teaching and Referral Hospital.
Methods: We systematically searched PubMed and EMBASE for articles describing chemotherapy treatment outcomes of ovarian epithelial cancer in low-resource settings. After data analysis, a secondary review was undertaken on randomized controlled trials (RCTs) aligning with chemotherapy availability in Kenya.
Results: We identified 1184 articles. Fourteen met our criteria: ovarian epithelial cancer, low resource, chemotherapy use, and survival or response data. No publications were RCTs or had a cohort larger than 100 patients. There was no consistency in drug choice between studies. After this search, we reviewed commonly quoted and relevant RCTs and meta-analyses conducted on ovarian cancer since the 1980s. Although RCTs in the developed world suggest carboplatin and taxol provide optimal survival benefit, these drugs are unavailable in Kenya. Cyclophosphamide and cisplatin provide the next most optimal survival benefit, with acceptable and manageable toxicity. Because these drugs are more available and affordable in Kenya, we have developed a protocol recommending their use, which has been accepted by the Moi Teaching and Referral Hospital.
Conclusions: Currently, there is a paucity of published RCTs that may guide treatment in low-resource settings. One considerable barrier to establishing and evaluating chemotherapy protocols in low-resource settings may be the cost of chemotherapy drugs. There needs to be an international movement to make cancer chemotherapeutics available at lower prices in low-resource settings.

Key Words: Chemotherapy, Developing countries, Guideline, Ovarian carcinoma, Review

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Ovarian cancer is the third most common gynecologic cancer and carries a high case fatality rate, with approximately 75% of patients presenting in advanced stages in Kenya. The current standard treatment includes surgery followed by combination chemotherapy: carboplatin and paclitaxel.[1] In some jurisdictions, bevacizumab has been added to first-line chemotherapy. None of these drugs are publicly available or affordable in Kenya.

In Kenya, an oncology group requested an evidence-based approach to care for ovarian cancer, which, in turn, would enable them to budget for the chemotherapy treatment of these patients. We established a group composed of both Kenyan and Canadian physicians and medical students to complete this task. To identify which feasible and affordable chemotherapy regimen may be most effective in treating advanced epithelial ovarian cancer in Kenya, a literature search evaluating outcome for chemotherapy in low-resource countries was performed.

METHODS

Two reviewers (L.S. and L.V.L.) systematically searched PubMed and EMBASE in January 2010 to identify research articles describing chemotherapy treatment outcomes of ovarian epithelial cancer in low-resource settings. (See text, Supplemental Digital Content 1, for search terms and criteria for study selection, http://links.lww.com/IGC/A30.) In addition, relevant randomized controlled trials (RCTs) that compared chemotherapeutics available and affordable in Kenya, including cisplatin, cyclophosphamide, and doxorubicin, were identified. Although these RCTs were conducted in resource-rich countries, they are a source of high-quality evidence that may be unavailable from low-resource settings.

Two reviewers (L.S. and J.N.) extracted information on chemotherapy regimen (dose and cycle length), number of patients, FIGO stage, inclusion criteria, response rate, survival, and toxicity. This information was used to develop an appropriate treatment protocol for the Moi Teaching and Referral Hospital (MTRH).

RESULTS

The systematic search of PubMed and EMBASE identified 1184 articles, of which 14 described the use of chemotherapeutics for the treatment of ovarian cancer. (See text, Supplemental Digital Content 1, for a list of these articles, http://links.lww.com/IGC/A30.) Eight studies described the use of drugs (eg, topotecan, carboplatin, taxol, etoposide, gemcitabine), which are not available at MTRH. All articles were single-arm studies, and none had more than 100 patients in the study. In most cases, the chemotherapeutic agents used in these studies are too expensive and are not available at MTRH. Only 2 studies were conducted in Africa. We decided that we could not apply information from these studies to the clinical situation at MTRH in Western Kenya, and therefore, these results were considered insufficient to guide protocol development.

The next approach we took was to search for studies that used drugs that are available in Kenya for the treatment of ovarian cancer. Cisplatin (P), cyclophosphamide (C), and doxorubicin (A) are available, and 9 RCTs were identified comparing different treatment schedules combining these drugs.[2–10] Results are summarized in Table 1.

The Gruppo Interregionale Cooperativo Oncologico Ginecologia compared single-agent cisplatin (P) against combination cisplatin/cyclophosphamide (CP) without and with doxorubicin (CAP).[2,3] After a 7-year follow-up, they reported slight but statistically nonsignificant differences in median survival of 19 versus 20 and 23 months, respectively, for P versus CP and CAP. They did report a statistically significantly improvement in progression-free survival when comparing CAP to CP (from 14.6 to 12.9 months).

Four other RCTs explored the benefit of adding doxorubicin to cisplatin/cyclophosphamide (CP vs CAP).[4–7] Although doxorubicin slightly improved median and progression-free survival, in 3 of 4 studies, this difference did not reach statistical significance for either outcome. In 1 study,[5] there was a longer median and progression-free survival for CAP, but the patient population was small, and there were large imbalances in performance status.

Although individual RCTs comparing CP versus CAP did not consistently demonstrate benefit from the addition of doxorubicin, a meta-analysis pooling 1194 patients from 4 studies detected a small, statistically significant, overall 6-year survival benefit with doxorubicin of 7% (54/606 alive with CP vs 68/588 with CAP).[11] Whether this survival benefit would translate to the Kenyan situation is unclear. In Kenya, the benefit from CAP needs to be balanced against limitations in providing optimal surgical care (debulking) and against the increased toxicity profile of adding doxorubicin. This issue is addressed later in this article.

The trials comparing CP versus CAP suggest a trend toward increased myelosuppression when doxorubicin is added, yet a meta-analysis was not done to establish significant differences in toxicity across these RCTs. One trial[2,3] reported significantly increased myelosuppression (leukopenia/thrombocytopenia), and 2 other trials[4,7] reported nonsignificant increases in leukopenia.

Several trials may guide a decision on the appropriate dosage. Two studies compared higher (100–120 mg/m^2) and lower doses (50–60 mg/m^2) of cisplatin in combination with cyclophosphamide (600–750 mg/m^2).[8,9] Although both RCTs reported that a higher dose of cisplatin improved survival and response rate, they also reported significant increases in myelosuppression, neurotoxicity, and ototoxicity. Sizes of both trials were small (50 and 165 patients), and one of them ended early. The Gynecologic Oncology Group subsequently conducted an RCT on 458 patients comparing a higher and a lower dose of CP (1000/100 vs 500/50 mg/m^2).[10] This study demonstrated that a higher dose of chemotherapy did not provide a statistically significant improvement in response rate or survival, and higher doses were associated with increased febrile and septic events as well as hematologic, renal, and gastrointestinal toxicities.

One study[12] showed that single-agent cisplatin (75 mg/m^2) offered similar survival and response rates compared with the cisplatin (50 mg/m^2)-cyclophosphamide (500 mg/m^2) combination. This study did not report on toxicity, and other studies on cisplatin dose intensity have demonstrated

increasing toxicity with increased dose.[8–10] In addition, it has been shown previously that cyclophosphamide does increase efficacy of single-agent platinum.[13]

In evaluation of several studies, CP (500/50 mg/m^2) provides an expected progression-free survival in the range of 9.5 to 22.7 months (median, 12.4 months) and a median survival of 15.9 to 22 months (median, 20 months).[2,4,6–10] The clinical, surgical, and pathological response rate for CP was reported as 58.0% (range, 54.4%–67.6%), 76.3%, and 56.3%, respectively.[2,4,6–7,10] These results are consistent with other RCTs that report comparable survival and response rates for CP.[14,15]

When deciding on the protocol, 2 drug characteristics played an important role in the considerations: toxicity and price. Limiting toxicity in a low-resource setting is very important because access to care and ability to manage events such as febrile neutropenia are limited. In the absence of advanced laboratory and intensive care facilities, drug toxicity will probably lead to more serious consequences including death. Severe adverse effects may also be unacceptable to patients, yet this has not been studied. A combination of cisplatin and cyclophosphamide in Western Kenya costs US $12 to $15 per cycle with the addition of doxorubicin adding US $20 per cycle to the cost.

On the basis of the above findings, in our opinion, 6 cycles of cisplatin (50 mg/m^2) combined with cyclophosphamide (500 mg/m^2) given every 21 days are suggested as the treatment of ovarian cancer at MTRH. Cisplatin (50 mg/m^2) combined with cyclophosphamide (500 mg/m^2) is expected to offer the optimal survival benefit, with a toxicity profile that is acceptable. The reported[10] frequencies of grade 3 or 4 toxicities for CP (500/50 mg/m^2) are as follows: 39% leukopenia, less than 1% thrombocytopenia, 0% febrile neutropenia, less than 2% sepsis/infection, less than 2% ototoxicity, and less than 1% neurotoxicity. There is also an advantage in cost by leaving out doxorubicin: a saving of approximately US $120 per 6 cycles of chemotherapy.

This literature review was presented at MTRH in a combined meeting that included medical oncology, gynecology, and pharmacy. The protocol was discussed at oncology rounds and was accepted and introduced into clinical practice.

TABLE 1. RCTs comparing cyclophosphamide (C), doxorubicin (A), cisplatin (P), or combinations at different doses

Author, yr	Regimen	Dose, mg/m^2	n	Clinical RR, %	Surgical RR, %	Pathol. RR, %	PFS, mo	MS, mo	Toxicity
GICOG,[2,3] 1992 (M)	P	50	174	—	20.0*	49.1	8.7	19.0	
	CP	650/50	182	—	21.0*	56.3	12.9	20.0	
	CAP	650/50/50	175	—	26.0*	66.3†	14.6†	23.0	Myelosuppression‡
Conte et al,[4] 1986 (M)	CP	600/50	63	54.4	76.3	—	12.5	22.4	
	CAP	600/45/50	62	55.6	81.1†	—	13.2	26.3	Myelosuppression
Hernadi et al,[5] 1988	CP	1000/60	16	62.5	—	—	3.5	12.5	—
	CAP	500/40/60	16	74.6	—	42.9*	12.5	26.5†	—
Bertelsen et al,[6] 1985 (M)	CP	500/60	135	67.6	—	20*	—	21.0	—
	CAP	500/40/60	132	74.6	—	28*	—	25.6	—
Omura et al,[7] 1989 (M)	CP	1000/50	176	30.2	—	—	22.7	—	
	CAP	500/50/50	173	32.8	—	—	24.6	—	Myelosuppression
Ngan et al,[8] 1989	CP	600/60	20	33.0	—	—	—	—	
	CP	600/120	30	55†	—	—	—	—	Myelosuppression‡ Neuro/ototoxicity‡
Kaye et al,[9] 1992	CP	750/50	79	34.0	—	—	9.5	15.9	Fever/sepsis‡ Myelosuppression‡ Renal/GI toxicity‡
	CP	750/100	80	61‡	—	—	19.6†	26.3‡	Fever/sepsis‡ Myelosuppression‡ Renal/GI toxicity‡
McGuire et al,[10] 1995	CP	500/50	235	60.0	—	—	12.1	19.5	
	CP	1000/100	223	55.0	—	—	14.3	21.3	Myelosuppression‡ Neurotoxicity‡
Marth et al,[12] 1998	P	75	93	63	—	—	11.9	21.5	—
	CP	500/50	83	52	—	—	10	19.4	—

*Complete response only.
†$P \leq 0.05$.
‡Significant (P not reported).
(M) indicates included in the meta-analysis; "—," not reported; GI, gastrointestinal; OS, overall survival; pathol., pathological; PFS, progression-free survival; RR, response rate.

DISCUSSION

Currently, there is a paucity of published RCTs that may inform ovarian cancer treatment in low-resource settings. Protocols based on RCTs conducted in high-resource settings will need to be assessed to ensure that they remain suitable for low-resource settings.

On the basis of the above findings, in our opinion, 6 cycles of cisplatin (50 mg/m^2) combined with cyclophosphamide (500 mg/m^2) given every 21 days are suggested as the treatment of ovarian cancer at MTRH. This recommendation is a judgment based on the efficacy of treatment balanced against toxicity. Two meta-analyses[13,16] from 1993 and 1995 provide evidence that the combination of cisplatin and cyclophosphamide is superior to single-agent cisplatin. The direct comparisons in RCTs do not show that the combination is significantly better.[12] Therefore, centers may choose single-agent cisplatin therapy based on simplicity and lower cost, and we do not have compelling evidence that outcomes will be inferior to our recommendation.

Several barriers may limit the feasibility of chemotherapy for advanced ovarian cancer in Kenya. Although the cost of combination cyclophosphamide/cisplatin is limited to US $75 for a complete treatment, this is still unattainable for many people in a country where the annual government health expenditure per capita is US $14.[17] Women treated at MTRH for now will not have to pay for their chemotherapy drugs. However, cost may remain a barrier as women must pay for the necessary laboratory tests that precede every chemotherapy treatment, for hospital admission if necessary, and for transport. A second barrier is the distance women must travel for treatment. Transport problems may delay the next course of chemotherapy. The MTRH is currently collecting information to assess the extent of this problem. A third barrier may be the local beliefs regarding the diagnosis of cancer. Women may seek out local treatment and not return for chemotherapy. More information will be needed to see how these and other obstacles will weigh in establishing a successful ovarian cancer treatment program.

At MTRH, costs of cisplatin and cyclophosphamide are covered by an external funding. In other low-resource settings, the costs of these agents remain prohibitively high. Consequently, there have been no studies to evaluate the success of these regimens, despite their vast promise and potential.

Cancer incidence is expected to rise during the next few decades, with the burden of disease shifting to low-income and middle-income countries. Having feasible and affordable treatment options available in these countries will become increasingly important. This article offers an example of how carefully weighing the appropriate evidence while taking the local situation into consideration may lead to a feasible and affordable treatment protocol for ovarian cancer. However, there will remain a gap in outcome between high-resource and low-resource countries unless the most effective treatments become universally available.

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