Int J Gynecol Cancer 2006, **16,** 1491–1497

SPECIAL ARTICLES

Gynecological cancers in developing countries: the challenge of chemotherapy in low-resources setting

S. BASILE*, R. ANGIOLI†, N. MANCI*, I. PALAIA*, F. PLOTTI* & P. BENEDETTI PANICI*
**Department of Obstetrics and Gynecology, La Sapienza University of Rome, Rome, Italy; and †Department of Obstetrics and Gynecology, Campus Bio-Medico University, Rome, Italy*

Abstract. Basile S, Angioli R, Manci N, Palaia I, Plotti F, Benedetti Panici P. Gynecological cancers in developing countries: the challenge of chemotherapy in low-resources setting. *Int J Gynecol Cancer* 2006; **16:**1491–1497.

The epidemiologic pattern of cancers in developing countries differs in many aspects from that of industrialized nations. Cancer natural history, microbiologic environment, patient's immune system, and drug availability may differ as well. Four of five new cases of cervical cancer and most of cervical cancer deaths occur in developing countries. Where chemoradiation and supportive care facilities are unavailable, it would be logical to consider an inexpensive effective drug. In locally advanced cases, neoadjuvant chemotherapy followed by surgery should be considered the treatment of choice. For ovarian cancer, it may be reasonable to maintain a secure supply of platinum and/or taxanes. For endometrial cancer, platinum compounds are proved active chemotherapic single agents. Oral medroxyprogesterone acetate (MPA) may represent a good chance for treating an advanced or recurrent disease. For vulvar/vaginal cancer, the role of chemotherapy alone is currently considered limited, and it is mostly used as palliative treatment in advanced or recurrent cases. Whenever possible, standard western chemotherapic regimens should be applied in developing countries as well. When standard therapies are unavailable, drugs of choice should be easily accessible, inexpensive, and effective. The most commonly used drugs are cisplatin, cyclophosphamide, and MPA.

KEYWORDS: chemotherapy, developing countries, gynecological cancer.

Developing countries present a peculiar cancer epidemiology, differing in many aspects from that of industrialized nations. The cause is mainly due to different population genetic patterns, lifestyles, sociocultural, and financial factors. This appears particularly true in gynecological oncology, where genetics and viruses assume a certain pathogenetic importance[1]. In a recent study conducted in Ghana, cervical cancer was the most frequent malignancy, constituting about 57.8% of gynecological cancers[2]. In these countries, diagnosis, management, and treatment options are faced with lack of resources, distance or difficult access to diagnostic facilities, and sometimes also the presence of educational, religious, and, primarily, economic barriers[3].

The availability and costs of anticancer drugs vary considerably in developing countries although, whenever possible, it would be recommended that the essential drugs for cancer chemotherapy identified by the World Health Organization be considered as first priority in securing a reliable drug supply[4]. Furthermore, it can easily happen that developing countries' health ministers invest a considerable part of the already scarce health resources on drugs of doubtful therapeutic efficacy[5]. Besides, anticancer drugs can be a double-edged sword since they are substantially cytotoxic agents with generally low-therapeutic indices, whose dosage and administration should be

Address correspondence and reprint requests to: Pierluigi Benedetti Panici, MD, Department of Obstetrics and Gynecology, La Sapienza University of Rome, Viale del Policlinico 155, 00169 Rome, Italy. Email: pierluigi.benedettipanici@uniroma1.it

doi:10.1111/j.1525-1438.2006.00619.x

carefully controlled to treat susceptible cancers without causing severe and sometimes permanent side effects, involving further resources waste.

Apart from the serious problem of drug availability that will inevitably influence physician, other factors must be considered in delivering chemotherapy for patients in developing countries. These include mainly skills in drugs administration, access to blood investigations and support, and effective antiemetic treatment; in fact, it is noteworthy that supporting therapies are sometimes crucial when administering such drugs, so a well-trained medical team should cooperate in order to prevent or manage toxicity.

Chemotherapic schedules are based on the experience of decades of clinical trials performed in affluent western nations, so it should not be assumed that their results could be equally applied in developing countries, where the three determinants of the outcomes of chemotherapy, the treatment itself, the tumor, and the patient, may differ significantly[6].

In addition to genetic differences, both in the patient and in the tumor itself that may influence chemosensitivity and pharmacologic features[7–9], comorbidities such as tuberculosis, acquired immunodeficiency syndrome, chronic liver disease, or malnutrition can be responsible for a major impact on treatment tolerance in low-resource settings[10,11]. Moreover, chemotherapy outcome itself may also differ drastically if regimens are modified because certain drugs are unavailable or unaffordable, because of poor protocol adherence by the physician or patient, or because of excessive toxicity resulting from inadequate supportive medical care.

For many reasons, most of malignancies in the third world are likely to be diagnosed at a more advanced stage[12], and, moreover, many patients make their prognosis worse by failing to complete an adequate therapy or follow-up. Concerning this difficult state, Magrath has clearly defined the vicious cycle in which socioeconomic deprivation would lead to the need of higher and higher financial resources and more health structures and services[6].

In the western clinical studies, chemotherapy regimens tended, over time, to obtain the best cost-benefit ratio using more and more complex, intense, and consequently toxic agents, especially for treating an advanced disease. In poor countries on the other hand, various circumstances make a situation in which the simpler or less expensive regimen is usually and inappropriately administered, subconsciously or intuitively, in order to increase access to care by reducing both costs and toxicity. The main problem of this practice is that in most cases this use of drugs is based on any scientific evidence of efficacy, and without the proper knowledge of past trials experience, no guide can assure adopting a rational and feasible chemotherapic strategy. Thus, unfortunately, for most of these patients the treatment goal is still symptom control rather than disease control.

Cervical cancer

With 471,000 annual cases and 233,000 deaths in the world, cervical cancer represents the second most common malignancy affecting women worldwide[13] and the main cause of cancer mortality in less developed countries, usually presenting at an advanced stage[14]. Thus, four of five new cases and, above all, most of cervical cancer deaths occur in developing countries: the highest mortality rates are in western and southern Africa, southern and central America, Caribbean, and south-central Asia[15]. In Latin America, especially, the incidence rates in several cities are among the highest worldwide probably due to a particularly high frequency of risk factors and at the same time a low screening coverage for this mostly preventable cancer[16]. On the other side of the Atlantic, in Uganda, cervical cancer accounts for nearly one quarter of all female cancer cases. Moreover, it is easy to imagine that the available incidence rates are probably grossly underestimated[17]. Many studies have underlined the weight of sociocultural factors analyzing the epidemiology of cervical cancer. Recently, it was reported that in Nigeria 80% of patients had no formal education in a situation of very low socioeconomic level[18].

On this background, the infection of human papillomaviruses (HPVs) is obviously very important. The relations between preinvasive lesions of the cervix and invasive cancer have been fairly established, and risk factors are mainly linked to sexual behavior and socioeconomic factors. Currently, etiology of the epidermoid histotype focuses on certain HPVs clearly recognized as carcinogenic.

Early cervical carcinoma is equally treated by radical surgery or radiotherapy, while in locally advanced cancer, radiotherapy is commonly used. Concerning treatment facilities for cervical cancer, consideration must be given that access to radiation services may be limited or nonexisting in most developing countries. In contrast, cervical cancer is currently considered a relatively chemosensitive tumor[19]. A promising approach for the management of locally advanced cervical cancer is neoadjuvant chemotherapy that, by inducing regression of tumor volume and its local spread, could make radical surgery feasible in most of these patients and could achieve sometimes a long-

term disease control[20]. It is noteworthy that most of the studies evaluating primary chemotherapy have been performed and promoted in European and Latin American countries, just where optimal radiation therapy is less frequently available to all population as compared to the United States and Canada. Thus, neoadjuvant chemotherapy represents often the most suitable therapeutic strategy to adopt in low-resources conditions, where radical hysterectomy remains a cost-effective treatment for most cervical cancer patients[21]. In surgical series including patients with FIGO stage I–IVA, an operability rate of 48–100% following primary chemotherapy was reported, without increased surgery-related morbidity. Pathologic complete responses were achieved in 9–27% of cases, and the incidence of lymph node metastases seemed to be markedly low[22].

The optimal chemotherapy in this setting is still unknown, but several studies suggest that cisplatin-based combinations may obtain higher tumor response rate than single agent cisplatin although with more side effects. Drug availability obviously influences selection of agents to administer with cisplatin. Gemcitabine, ifosfamide, cyclophosphamide, epirubicin, and bleomycin are the drugs most frequently associated. In particular, a cisplatin and gemcitabine regimen seems highly active and well tolerated in a neoadjuvant setting, with manageable toxicities, and this combination appears to compare favorably to all other cisplatin-based chemotherapy schedules[23]. Cisplatin is currently considered also the most effective single agent as palliative treatment in metastatic or recurrent disease[24].

On this background, in less developed countries where chemoradiation and supportive care facilities are often unavailable, it would be logical to consider a cheap and simple cisplatin-based regimen. Since some data indicate that a dose rate greater than 20 mg per week of cisplatin is more effective than lower dosages[14,25], and a schedule of cisplatin 100 mg/mq every 3 weeks could achieve a good efficacy without excessive toxicity, this single-agent regimen could be applied also in a neoadjuvant setting or as adjuvant treatment if radiotherapy is not accessible. Where radiation facilities exist, evidence favoring combined chemoradiation in management of locally advanced cervical cancer is compelling, and the simplest regimen and one least likely to cause severe side effects is cisplatin 40 mg/m^2 weekly during radiation.

Regarding small cell neuroendocrine carcinoma, preoperative chemotherapy with vincristine, bleomycin, and cisplatin was demonstrated to be a useful therapeutic tool to improve the resectability of large tumors and to improve the outcome[26].

In conclusion, in these cases, neoadjuvant chemotherapy followed by surgery should be considered the treatment of choice in countries or conditions in which concurrent chemoradiotherapy cannot be delivered optimally in terms of drugs and prevention or management of side effects[27].

Ovarian cancer

Ovarian cancer has the highest case fatality rate among gynecological tumors worldwide because of lack of effective screening methods and nonspecific early-warning symptoms. In a recent study performed in Nigeria, it represented the third most common gynecological tumor, with 9.8% of 214 cases. Eighty-one percent presented at III and IV FIGO stages, but only 23.8% underwent platin-based adjuvant chemotherapy[28]. Primary treatment for all stages of resectable disease usually consists of maximal cytoreductive surgery, but some forms of neoadjuvant chemotherapy are currently under evaluation[29].

Platinum compounds, up to an optimal dose intensity, represent currently the core of first-line chemotherapy to administer after cytoreduction in case of advanced ovarian adenocarcinoma because of the high risk of relapse and the poor 5-year survival rates[30–34]. Ovarian cancer was one of the first solid malignancies to be treated by chemotherapy: cyclophosphamide, melphalan, and chlorambucil were used until the mid-1970s.

Since then, the platinum compounds have become the cornerstone of chemotherapy for women with advanced disease. International Collaborative Ovarian Neoplasm-2[35] trial demonstrated the same results in terms of progression-free and overall survivals between cyclophosphamide, doxorubicin, and cisplatin (CAP) against carboplatin alone.

A further Gynecologic Oncology Group trial (GOG-132) in suboptimally debulked patients, compared cisplatin alone, 24-h infusion paclitaxel and the combination of paclitaxel followed by cisplatin, cisplatin alone, or in combination yielded superior response rates and progression-free survival compared to paclitaxel[36]. As a consequence, most authors suggested paclitaxel plus cisplatin as standard first-line treatment[37]. However, due to the neurotoxicity of paclitaxel plus cisplatin and the evidence of the approximate equivalence of cisplatin and carboplatin from meta-analyses[38], many centers have used paclitaxel and carboplatin (area under curve 4–7)[37]. Further data showed that single agent carboplatin and CAP are as effective as paclitaxel plus carboplatin as first-line treatment. The favorable toxicity profile of single agent carboplatin suggests that this drug represents

a rational first-line chemotherapy[39]. On this background, considering low-resources conditions, it may be reasonable to maintain a secure supply of platinum and/or taxanes.

In conclusion, if standard carboplatin–taxol is not feasible, either cisplatin (100 mg/mq) or carboplatin alone (AUC 4-7) could represent valid alternative therapeutic options. Cyclophosphamide added to platinum or as single agent in absence of platin compounds can also be considered. More complex multidrug regimens including gemcitabine are not likely to be feasible in low-resources setting. Topotecan, such as anthracyclines, seems unaffordable for most developing countries[40,41].

Endometrial cancer

Endometrial cancer has a low incidence in the third world, as most other hormone-dependent tumors[1]. International variation in endometrial cancer rates may reflect the differences in distribution of known risk factors, like familiarity, obesity, diabetes, ovarian dysfunction, infertility, nulliparity, and tamoxifen use. In Gabon, during the 1990s, the reported incidence of this carcinoma was 5.3%, with adenocarcinoma being the most frequent histotype (79.4%)[42]. Fortunately, mostly because of vaginal bleeding, several patients with endometrial cancer can have an early diagnosis, and therefore, they can benefit from a prompt treatment[2,43].

When a physician in a developing country decides on chemotherapy, the same issues matter: availability and affordability of drugs and their dose-limiting toxicity profile. Doxorubicin, one of the most studied single agents for endometrial cancer[44] due to its low-therapeutic indices, potential cardiac toxicity, and, above all, the high cost, is not used in most poor resources countries. Another anthracycline, epirubicin, could represent a valid alternative for its more favorable toxicity profile and, at the same time, a demonstrated response rate of 26% in advanced or recurrent endometrial cancer[45]. Other agents, such as 5-fluorouracil, with general good tolerance and affordability, need further studies to confirm their efficacy[46].

Platinum compounds cisplatin and carboplatin are proven active chemotherapic single agents for endometrial cancer. Cisplatin as first-line chemotherapy has shown a 21% response, while carboplatin (at 300–400 mg/mq) has demonstrated an overall response rate ranging from 29% to 33%[47,48]. Combination chemotherapy analysis demonstrated that platinum agents and doxorubicin would represent a good choice in the treatment of advanced endometrial cancer and also paclitaxel combined with fixed doses of platin confirmed high response rates[49].

Oral medroxyprogesterone acetate (MPA) at 200 mg/day, with its proved activity (overall response rate of 18%) and easy pharmacologic management, may represent a good chance for treating an advanced or recurrent disease also in developing countries[50].

The first large Gynecologic Oncology Group trial evaluating oral progestins in patients with advanced or recurrent disease showed an overall response rate of 18%, with short median progression-free and overall survival times, 4 and 10.5 months, respectively[51]. This finding was confirmed in a second trial where patients were randomized to receive oral MPA 200 mg/day or 1,000 mg/day. The objective of this study was to determine if higher doses of the progestin would be associated with an increased response rate. The overall response rate was 25%, with similar results in both groups. The authors concluded that MPA 200 mg/day is active as an initial agent in the treatment of advanced or recurrent endometrial cancer[51].

It is important to make certain of the presence of estrogen and progesterone receptors since patients with tumor receptors positive are more likely to respond to MPA therapy than those without receptor[51]. Also tamoxifen and anastrozole should be probably more considered in those patients, taking into account the above-described disease molecular patterns[52,53].

Vulvar and vaginal cancers

Vulvar and vaginal cancers are relatively rare tumors in developing countries, as well as in the western world, and affect mostly women at advanced age. Vulvar carcinoma in general accounts for only 5% of all genital malignancies[54], and more than 80% of cases are represented by squamous cell histotype[55], while vaginal cancer is even more rare than the vulvar cancer, accounting for just 1–2% of all genital tract tumors. Data about the incidence and characteristics of these malignancies in the third world are very scarce at the moment.

Both neoplastic precursors, vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia, respectively, in vulvar and vaginal carcinoma, are well-investigated preinvasive dysplasic lesions, currently considered with a potential capacity to heal if clearly diagnosed and treated. These two malignancies, at least the most frequent squamous cell histologic variants, share the same risk factors of cervical carcinoma, ie, HPV-associated lesions, number of sexual partners, low socioeconomic status, and smoking.

Currently, both vulvar and vaginal cancers are mainly treated with surgery and radiotherapy (external and brachytherapy)[56], even if, in the future,

chemoradiotherapy (neoadjuvant or alone) is likely to play a more and more important role in the management of these malignancies as in cervical cancer[14].

Vulvar cancer has been historically considered a chemoresistant tumor[57] until, since 1990, some European Organization for Research and Treatment of Cancer trials demonstrated the efficacy of chemotherapy in advanced vulvar cancer cases[58,59]. The role of chemotherapy alone, even if actually poorly studied, is currently considered limited, mostly as palliative treatment in advanced or recurrent cases, demonstrating a good efficacy in terms of relief from disease symptoms[60].

In this setting, published data are still scarce to indicate a possibly single-drug regimen with both a proved efficacy and limited side effects; thus, in our opinion, the choice of chemotherapy should be done considering local availability of drugs with some evidence of efficacy in any setting. Combined chemotherapy with cisplatin and 5-fluorouracil, even if followed by pelvic irradiation, obtained a 75% response rate in stage III and 50% in stage IV patients without severe toxicities[61].

A high incidence of toxicity with the use of chemoradiation comprising 5-fluorouracil and mitomycin C has been recently reported for primary, adjuvant, and salvage therapy for vulvar cancer[62].

Concerning neoadjuvant chemotherapy, in order to make radical surgery feasible in primary unresectable disease, the drugs studied in the 1980s in such setting are cisplatin, bleomycin, and methotrexate, but probably the reported poor response rate was related to the advanced disease (FIGO stage IVA)[60]. The chemotherapic role as adjuvant treatment in node-positive vulvar malignancies has been recently reconsidered[63].

This seems one of the recent most important topics to evaluate in the context we are focusing. The current gold standard of postoperative therapies for vulvar cancer remains radiation, indicated in node-positive patients. Unfortunately, it is associated, especially if not properly performed, with severe complications such as local irritation, desquamation, pain, and lymphedema, which are sometimes very difficult to manage[64].

Whenever possible in these countries, adjuvant chemotherapy instead of radiation could minimize complications without jeopardizing cancer treatment and moreover would reserve radiotherapy, if available, in case of failure. However, data on this topic are still lacking, and further studies are needed to prove the efficacy of adjuvant chemotherapy for these patients. In absence of strong data supporting the higher efficacy of a polychemotherapy, we would suggest the adoption of a monochemotherapy regimen. Cisplatin, at the dosage of 100 mg/mq intravenously every 3 weeks (eventually reduced of 25% if needed), with its proven efficacy in this setting, seems to represent currently a good chance of postoperative treatment.

Conclusion

One way in which cancer treatment outcomes could be improved and, at the same time, both chemorelated toxicity and costs reduced, would be the implementation of successful healthcare programs focused on earlier diagnosis. An early diagnosis and a prompt treatment make it possible to avoid subsequent higher costs, also reducing duration of treatment. In the meantime, it happens that the only feasible way of reducing the cost of chemotherapy is to give lower dosages or to use cheaper drugs. In developing countries, particularly, chemotherapy should be properly tailored for each patient considering the available resources[6]. Patients with an impaired renal, hepatic, or cardiac function should be accurately monitored, and the choice of chemotherapic regimen should take all these problems into account as well.

Whenever possible, standard western chemotherapic regimens should, in general, be applied also in developing countries, at least until further well-performed trials in those areas will debate current results in terms of disease-free and overall survival and quality of life. When the context of patient condition or health resources makes it difficult or dangerous to perform efficacious combination chemotherapy, a single-agent regimen should, in general, be applied.

Residency programs in western medical schools could provide for structured periods of clinical assistance in a "sister" developing country, where chemotherapic and related drugs (epoetin alfa, granulocyte colony–stimulating factors, cortisones for managing both nausea and hypersensitivity reactions, and gastric protectors) could be easily and conveniently used in the context of clinical trials.

Persistent efforts are ethically mandatory in order to sensitize people promoting in the scientific community a context of regulation in which clinical trials programs provide for including also these populations. Therefore, valid "international groups" should include in ongoing trials also these patients, improving condition and quality of treatment of many patients on one hand and, at the same time, achieving a benefit for the global scientific progress and so for patients everywhere—a research therefore based not only on science but also on ethics for a world that travels toward globalization.

As Wilimas[65] wisely said, "Science may know no boundaries, but, unfortunately, affluence does". More

and more collaboration between developed and developing countries will significantly contribute to overcome these problems, as well as open up new research opportunities in countries that presently carry so much of the global cancer burden.

The right answer to the consequent perplexity is to paraphrase George Bernard Shaw: "The problems of our world cannot be solved by sceptics and cynics whose horizons are limited by obvious realities. We need women and men who can dream of things that never were, and ask why not"[66].

References

1 Tkeshelashvili VT, Bokhman JV, Kuznetzov VV, Maximov SJ, Chkuaseli GT. Geographic peculiarities of endometrial and cervical cancer incidence in five continents (review). *Eur J Gynaecol Oncol* 1993;**14:**89–94.
2 Nkyekyer K. Pattern of gynaecological cancers in Ghana. *East Afr Med J* 2000;**77:**534–8.
3 Sandelin K, Apffelstaedt JP, Abdullah H, Murray EM, Ajuluchuku EU. Breast Surgery International—breast cancer in developing countries. *Scand J Surg* 2002;**91:**222–6.
4 Sikora K, Advani S, Koroltchouk V *et al*. Essential drugs for cancer therapy: a World Health Organization consultation. *Ann Oncol* 1999;**10:**385–390.
5 Homedes N, Ugalde A, Chaumont C. Scientific evaluations of interventions to improve the adequate use of pharmaceuticals in Third World countries. *Public Health Rev* 2001;**29:**207–30.
6 Magrath I. Chemotherapy in developing countries—is less better? *Eur J Cancer* 2003;**39:**1497–500.
7 Taningher M, Malacarne D, Izzotti A, Ugolini D, Parodi S. Drug metabolism polymorphisms as modulators of cancer susceptibility. *Mutat Res* 1999;**436:**227–61.
8 Krajinovic M, Labuda D, Sinnett D. Childhood acute lymphoblastic leukemia: genetic determinants of susceptibility and disease outcome. *Rev Environ Health* 2001;**16:**263–79.
9 Flatt PM, Pietenpol JA. Mechanisms of cell-cycle checkpoints: at the crossroads of carcinogenesis and drug discovery. *Drug Metab Rev* 2000;**32:**283–305.
10 Advani SH, Giri NK, Pai SK *et al*. Acute lymphoblastic leukemia in childhood: treatment, results and prognostic factors. *Indian J Cancer* 1989;**26:**180–8.
11 Odida M, Schmauz R, Lwanga SK. Grade of malignancy of cervical cancer in regions of Uganda with varying malarial endemicity. *Int J Cancer* 2002;**99:**737–41.
12 Gaitonde K, Goyal A, Nagaonkar S, Patil N, Singh DR, Srinivas V. Retrospective review and long-term follow-up of radical cystectomy in a developing country. *BJU Int* 2002;**89**(Suppl. 1):57–61.
13 Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;**2:**533–43.
14 Green JA, Kirwan JM, Tierney JF *et al*. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;**358:** 781–6.
15 Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999;**83:**18–29.
16 Eluf-Neto J, Nascimento CM. Cervical cancer in Latin America. *Semin Oncol* 2001;**28:**188–97.
17 Schmauz R, Owor R. Epidemiological aspects of cervical cancer in tropical Africa. *IARC Sci Publ* 1984;**63:**413–31.
18 Emovon AC. Sociocultural factors associated with cervical cancer in Bendel State, Nigeria. *Int J Gynaecol Obstet* 1977;**15:**253–5.
19 Friedlander M, Kaye SB, Sullivan A *et al*. Cervical carcinoma: a drug-responsive tumor—experience with combined cisplatin, vinblastine, and bleomycin therapy. *Gynecol Oncol* 1983;**16:**275–81.
20 Benedetti-Panici P, Greggi S, Colombo A *et al*. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. *J Clin Oncol* 2002;**20:**179–88.
21 Rocconi RP, Estes JM, Leath CA III, Kilgore LC, Huh WK, Straughn JM Jr. Management strategies for stage IB2 cervical cancer: a cost-effectiveness analysis. *Gynecol Oncol* 2005;**97:**387–94.
22 Serkies K, Jassem J. Chemotherapy in the primary treatment of cervical carcinoma. *Crit Rev Oncol Hematol* 2005;**54:**197–208.
23 Termrungruanglert W, Tresukosol D, Vasuratna A, Sittisomwong T, Lertkhachonsuk R, Sirisabya N. Neoadjuvant gemcitabine and cisplatin followed by radical surgery in (bulky) squamous cell carcinoma of cervix stage IB2. *Gynecol Oncol* 2005;**97:**576–81.
24 Omura GA. Chemotherapy for stage IVB or recurrent cancer of the uterine cervix. *J Natl Cancer Inst Monogr* 1996;**21:**123–6.
25 Chang HC, Lai CH, Chou PC *et al*. Neoadjuvant chemotherapy with cisplatin, vincristine, and bleomycin and radical surgery in early-stage bulky cervical carcinoma. *Cancer Chemother Pharmacol* 1992;**30:**281–5.
26 Sevin BU, Method MW, Nadji M, Lu Y, Averette HA. Efficacy of radical hysterectomy as treatment for patients with small cell carcinoma of the cervix. *Cancer* 1996;**77:**1489–93.
27 Benedetti Panici P, Scambia G, Baiocchi G *et al*. Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. *Cancer* 1991;**67:**372–9.
28 Odukogbe AA, Adebamowo CA, Ola B *et al*. Ovarian cancer in Ibadan: characteristics and management. *J Obstet Gynaecol* 2004;**24:**294–7.
29 Warwick J, Kehoe S, Earl H, Luesley D, Redman C, Chan KK. Long-term follow-up of patients with advanced ovarian cancer treated in randomised clinical trials. *Br J Cancer* 1995;**72:**1513–7.
30 Levin L, Simon R, Hryniuk W. Importance of multiagent chemotherapy regimens in ovarian carcinoma: dose intensity analysis. *J Natl Cancer Inst* 1993;**85:**1732–42.
31 McGuire WP, Hoskins WJ, Brady MF *et al*. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 1995;**13:**1589–99.
32 Kaye SB, Paul J, Cassidy J *et al*. Mature results of a randomized trial of two doses of cisplatin for the treatment of ovarian cancer. Scottish Gynecology Cancer Trials Group. *J Clin Oncol* 1996;**14:**2113–9.
33 Jodrell DI, Egorin MJ, Canetta RM *et al*. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol* 1992;**10:**520–8.
34 Gore M, Mainwaring P, A'Hern R *et al*. Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. *J Clin Oncol* 1998;**16:**2426–34.
35 ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. International Collaborative Ovarian Neoplasm Study. *Lancet* 1998;**352:**1571–6.
36 Muggia FM, Braly PS, Brady MF *et al*. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2000;**18:**106–15.
37 Piccart MJ, Bertelsen K, James K *et al*. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;**92:**699–708.
38 Advanced Ovarian Cancer Trialist Group. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. *Br J Cancer* 1998;**78:** 1479–87.
39 International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002;**360:**505–15.
40 Ten Bokkel Huinink W, Gore M, Carmichael J *et al*. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol* 1997;**15:**2183–93.
41 Gordon A, Carimcheal J, Malfetno J *et al*. Final analysis of a phase III, randomized study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. International Topotecan Study Group. *Proc Am Soc Clin Oncol* 1998;**17:**356a.
42 Meye JF, Mabicka BM, Belembaogo E, Minko-Mi-Etoua DI, Engongah-Beka T, Minko-Mi-Etoua D. Endometrial carcinomas in Gabon. A study of 34 cases in 11 years: 1988–1998. *Sante* 2000;**10:**43–5.
43 Briggs ND, Katchy KC. Pattern of primary gynecological malignancies as seen in a tertiary hospital situated in the Rivers State of Nigeria. *Int J Gynaecol Obstet* 1990;**31:**157–61.

44 Thigpen JT, Blessing JA, DiSaia PJ, Yordan E, Carson LF, Evers C. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 1994;**12:**1408–14.

45 Calero F, Asins-Codoner E, Jimeno J *et al*. Epirubicin in advanced endometrial adenocarcinoma: a phase II study of the Group Ginecologico Espaniol para el Tratamiento Oncologico (GGETO). *Eur J Cancer* 1991;**27:**864–6.

46 Broun GO, Blessing JA, Eddy GL, Adelson MD. A phase II trial of vincristine in advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group Study. *Am J Clin Oncol* 1993;**16:**18–21.

47 Thigpen T, Vance RB, Khansur T. The platinum compounds and paclitaxel in the management of carcinomas of the endometrium and uterine cervix. *Semin Oncol* 1995;**22**(5 Suppl. 12):67–75.

48 Burke TW, Munkarah A, Kavanagh JJ *et al*. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. *Gynecol Oncol* 1993;**51:**397–400.

49 Muss HB. Chemotherapy of metastatic endometrial cancer. *Semin Oncol* 1994;**21:**107–13.

50 Thigpen T, Blessing J, DiSaia P. Oral medroxyprogesterone acetate in advanced or recurrent endometrial carcinoma: results of therapy and correlation with estrogen and progesterone receptor levels—The Gynecologic Oncology Group experience. In: Baulier E, Iacobelli S, McGuire W, eds. *Endocrinology and malignancy.* New York, NY: Parthenon Publishers, 1986:446–54.

51 Thigpen JT, Brady MF, Alvarez RD *et al*. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol* 1999;**17:**1736–44.

52 Deppe G, Cohen CJ, Bruckner HW. Treatment of advanced endometrial adenocarcinoma with cis-dichlorodiammine platinum (II) after intensive prior therapy. *Gynecol Oncol* 1980;**10:**51–4.

53 Lhomme C, Vennin P, Callet N *et al*. A multicenter phase II study with triptorelin (sustained-release LHRH agonist) in advanced or recurrent endometrial carcinoma: a French anticancer federation study. *Gynecol Oncol* 1999;**75:**187–93.

54 DiSaia PJ, Creasman WT. Invasive carcinoma of the vulva. In: *Clinical gynaecologic oncology.* DiSaia PJ *et al*, 5th eds, St. Louis, MO: Mosby-Year Book, 1997:202–32.

55 Chi DS. The diagnosis and management of vulvar cancer. *Prim Care Update Ob Gyns* 1999;**6:**24–32.

56 Beller U, Sideri M, Maisonneuve P *et al*. Carcinoma of the vulva. *J Epidemiol Biostat* 2001;**6:**155–73.

57 Deppe G, Cohen CJ, Bruckner HW. Chemotherapy of squamous cell carcinoma of the vulva: a review. *Gynecol Oncol* 1979;**7:**345–8.

58 Durrant KR, Mangioni C, Lacave AJ *et al*. Bleomycin, methotrexate, and CCNU in advanced inoperable squamous cell carcinoma of the vulva: a phase II study of the EORTC Gynaecological Cancer Cooperative Group (GCCG). *Gynecol Oncol* 1990;**37:**359–62.

59 Wagenaar HC, Colombo N, Vergote I *et al*. Bleomycin, methotrexate, and CCNU in locally advanced or recurrent, inoperable, squamous-cell carcinoma of the vulva: an EORTC Gynaecological Cancer Cooperative Group Study. European Organization for Research and Treatment of Cancer. *Gynecol Oncol* 2001;**81:**348–54.

60 Benedetti-Panici P, Greggi S, Scambia G, Salerno G, Mancuso S. Cisplatin (P), bleomycin (B), and methotrexate (M) preoperative chemotherapy in locally advanced vulvar carcinoma. *Gynecol Oncol* 1993;**50:**49–53.

61 Tyring SK. Vulvar squamous cell carcinoma: guidelines for early diagnosis and treatment. *Am J Obstet Gynecol* 2003;**189**(Suppl. 3):S17–23.

62 Mulayim N, Foster Silver D, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. *Gynecol Oncol* 2004;**93:**659–66.

63 Bellati F, Angioli R, Manci N *et al*. Single agent cisplatin chemotherapy in surgically resected vulvar cancer patients with multiple inguinal lymph node metastases. *Gynecol Oncol* 2005;**96:** 227–31.

64 Peh WC, Khong PL, Sham JS, Ho WY, Yeung HW. Sacral and pubic insufficiency fractures after irradiation of gynaecological malignancies. *Clin Oncol* (R Coll Radiol) 1995;**7:**117–22.

65 Wilimas JA, Ribeiro RC. Pediatric hematology-oncology outreach for developing countries. *Hematol Oncol Clin North Am* 2001;**15:** 775–87.

66 Murray EM. Medical and radiation oncology for breast cancer in developing countries with particular reference to locally advanced breast cancer. *World J Surg* 2003;**27:**924–7.

Accepted for publication February 7, 2006