Preliminary Study on the Effect of Treatment with Pegylated Liposomal Doxorubicin for Persistent and Recurrent Ovarian Cancer and Uterine Malignancies

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Patients with advanced ovarian cancer or any uterine malignancy who have failed first-line treatment with combination chemotherapy have few options left for progression-free survival. One of the promising second line treatments is pegylated liposomal doxorubicin. **Objective**: The main purpose of the study was to determine the response rate and toxicity profile of pegylated liposomal doxorubicin from 2000-2005 was conducted at the UP-PGH Cancer Institute. **Results**: Eight patients were included in the study. There were three cases of ovarian malignancy and five cases of uterine malignancies who had prior treatment with chemotherapy or radiotherapy and had progressive or recurrent disease. Grade 3-4 hematologic, renal and cardiac toxicities were not to occur after the second to the fourth course of pegylated liposomal doxorubicin. All had progression of disease after treatment with pegylated liposomal doxorubicin. The mean time to disease progression was 2 months. The mean overall survival in four documented cases was 4 months. **Conclusion**: Pegylated liposomal doxorubicin is a promising second-line treatment for progressive and recurrent ovarian and uterine malignancies. Its ease of administration and provision of a progression-free survival period outweighs the mild to moderate form of toxicities it can cause.

Key words: pegylated liposomal doxorubicin, toxicity profile, disease progression

Gynecologic malignancies comprise approximately 19.7 percent of all female cancers in the Philippines.[1] Doxorubicin plays an important role in the adjuvant setting not only for endometrial cancer, but also for ovarian and cervical cancers. Unfortunately, because of its toxicity profile, its use either as a single agent or as part of a combination regimen is limited.

Pegylated liposomal doxorubicin is a new formulation of doxorubicin, which has enhanced therapeutic efficacy with reduced toxicity. Most of the studies on pegylated liposomal doxorubicin are performed on ovarian carcinomas as second-line therapy. Phase II studies by Muggia, et al.[2] and Gordon, et al.[3] show response rates of 26 percent and 17 percent, respectively, for relapsed ovarian cancer. Most common toxicities encountered are palmar-plantar erthrodysesthesia (PPE) and stomatitis. Interim analysis of phase III randomized trial by Gordon, et al.[4] comparing pegylated liposomal doxorubicin versus topotecan shows a comparable response rate but pegylated liposomal doxorubicin displays a more favorable toxicity profile.

Pegylated liposomal doxorubicin may also play a role in the adjuvant treatment of endometrial and cervical cancers. However, in contrast to ovarian,

most of these cases may have received prior radiation therapy, resulting in decreased tolerance in chemotherapy. A phase II study by Israel, et al.[5] shows the safety of pegylated liposomal doxorubicin administration to previously irradiated patients.

The introduction of pegylated liposomal doxorubicin, a novel liposomal formulation of doxorubicin stabilized with surface-bound molecules of the hydrophilic polymer methoxypolethylene glycol (STEALTH liposome), is a significant contribution in the treatment of ovarian cancer. While doxorubicin as an anthracycline has long been used in the treatment of ovarian cancer as a first line agent together with cisplatinum, the treatment response has been challenged repeatedly. Initially, in four different randomized trials, the doxorubicin-containing arm failed to demonstrate a survival advantage; with its inclusion leading to increased toxicity. However, a meta-analysis of these trials confirms a survival advantage to the doxorubicin-containing arm. This result has stimulated interest in further work with doxorubicin for ovarian cancer treatment.

Pegylated liposomal doxorubicin has a significantly different pharmacologic profile from the native drug due to the long-circulating polyethylene glycol-coated liposomal formulation of doxorubicin hydrochloride. The protective coat of the drug is a hydrophilic polymer that reduces the interaction between the drug and the plasma components. With this feature, the drug stays longer in circulation similar to a prolonged infusion. It also allows the drug to penetrate through defective tumor vessels as an intact liposome and over a prolonged period there is accumulation of the drug in the tumor tissue.

In conditions where the use of first-line agents like carboplatin and paclitaxel manifest resistance or refractoriness, pegylated liposomal doxorubicin may be used as a second line single-agent, cytotoxic drug. It is therefore important to closely monitor response of the ovarian tumor to the first two or three cycles of carboplatin and paclitaxel. Especially among cases where the tumor residual is sub-optimum or bigger than 2 cm, the diminution in the size of the tumor, as measured by computerized tomography should guide the oncologist in shifting to a second line agent such as pegylated liposomal doxorubicin. Any delayed diminution in CT scan measurements after the second and the fourth cycle should make the oncologist considering shifting to a second line agent.

Phase II studies demonstrate the efficacy of pegylated liposomal doxorubicin in relapsed ovarian cancer.[2,3] The recent publication of the Phase III trial[4] comparing the use of pegylated liposomal doxorubicin versus topetecan as second line agents in platinum/paclitaxel resistant ovarian cancer proves the superiority of pegylated liposomal doxorubicin. It shows a comparable efficacy, a convenient administration schedule and favorable safety profile. It is easy to administer in the outpatient clinic and it has no severe toxicities that usually accompany topotecan.

In addition, there are many studies[5-9] that show the efficacy of pegylated liposomal doxorubicin in the treatment of solid uterine malignancies with high grade features. Sarcomas, undifferentiated carcinomas, small cell tumors, clear cell tumors as well as neuroendocrine tumors in the corpus and cervix may benefit from treatment with pegylated liposomal doxorubicin in combination with cisplatinum.

It is therefore an improvement of progression-free survival that each patient is afforded with the introduction of pegylated liposomal doxorubicin in the Philippines. While the aims in treatment of recurrent/resistant diseases may be palliative, and the quality of life may have been the modest goal in the past, the introduction of pegylated liposomal doxorubicin has stretched the goals of treatment to longer progression-free survival.

The main objective of this study was to determine the response rate and toxicity profile of pegylated liposomal doxorubicin as a single agent for persistent and recurrent ovarian and uterine malignancies.

Materials and Methods

Patient Population

This study included gynecologic cancer patients who had persistent or recurrent ovarian cancer or

uterine malignancy who received the pegylated liposomal doxorubicin (PLD) from 2000-2004 in a cancer institute of a tertiary hospital.

Inclusion Criteria

Patients meeting the following criteria were eligible for enrollment:

1. Patient is at least 18 years of age or more.
2. Patient has a histologically proven ovarian cancer or uterine malignancy.
3. Patient has a documented case of persistent or recurrent ovarian cancer or uterine malignancy by appropriate radiologic imaging (X-ray, ultrasound, CT scan, MRI)
4. Patient must have measurable or evaluable disease
5. Patients must not have received prior treatment of pegylated liposomal doxorubicin
6. Patient has an ECOG performance score of 0-2 (Appendix A)
7. Patient has a life expectancy >3 months
8. Patient has normal electrocardiography
9. Patient has normal organ function, except if abnormal due to tumor involvement.
   Normal bone marrow function as indicated:
   Platelet $\geq$ 100,000 mm^3
   Hemoglobin $\geq$ 10 g/dl
   Neutrophil > 1.5 x $10^3/mm^3$
   Adequate renal function as indicated by:
   Serum creatinine <2.5 mg/dl
   Adequate liver function as indicated by:
   Bilirubin and AST or ALT <2 times the upper limit of normal unless related to primary disease
10. Patient has written informed consent

Exclusion Criteria

Patients were not enrolled if the following criteria applied:

1. Patients who received prior pegylated liposomal doxorubicin treatment of a gynecologic malignancy.
2. Patient is pregnant or is breastfeeding.
3. Patient is hypersensitive to anthracycline therapy.
4. Patient has a history of cardiac disease, with New York Heart Association Class II or greater (Appendix B) with congestive heart failure.
5. Patient has a clinically significant hepatic disease.
6. Patient has uncontrolled bacterial, viral or fungi infection.
7. Patient exhibits confusion or disorientation.
8. Patient has any condition (medical, social and psychosocial) which would prevent adequate follow-up.
9. Patient has received radiotherapy in the last 4 weeks.
10. Patient has any other active primary tumor, underwent treatment, except basal or squamous cell carcinoma of the skin or carcinoma in situ.
11. Patient has symptomatic metastasis to the brain.
12. Patient has received prior radiation therapy to more than one third of the hematopoeitic sites.
13. Patient has received poor biologic response modifiers or any other investigational drugs.

Methodology

A retrospective review of medical records of gynecologic cancer patients who received pegylated liposomal doxorubicin as a single agent for persistent or recurrent ovarian cancer or uterine malignancy from 2000 to 2004 was done. Demographic data such as age, gravidity, parity, body mass index, menarche, vices and use of oral contraceptive pill use was noted.

For second line or salvage treatment of ovarian cancer, pegylated liposomal doxorubicin was given as a single agent. It was administered at 40 mg/m^2 as a 1 hour intravenous infusion in 250 cc of D5W every three weeks for six cycles. Pegylated liposomal doxorubicin as a single agent may be given without hydration or anti-emetics.

For endometrial cancer or uterine sarcomas, as well as cervical adenocarcinomas or poor histologic types, pegylated liposomal doxorubicin was given as a single agent. Pegylated liposomal doxorubicin was administered at 40 mg/m^2 as a 1 hour intravenous infusion in 250 cc of D5W, with or without hydration and anti-emetics, every three weeks.

The dose limiting toxicity of pegylated liposomal doxorubicin is palmar-plantar erythrodysesthesia (PPE). These adverse reactions were assessed carefully prior to administration of the next cycle. Increasing the length of the cycle was the optimum method for avoiding subsequent occurrence of the PPE.

Serious events occurring most frequently with cisplatin were bone marrow suppression, peripheral neuropathy and renal toxicity.

Active follow up included physical and pelvic examinations, laboratory tests and evaluation of adverse reactions. The following laboratory examinations were performed prior to each cycle: complete blood count, serum BUN, creatinine, AST, ALT, alkaline phosphatase and total bilirubin. Cardiac status was assessed by electrocardiography (ECG) within 4 weeks prior to start of study and prior to start of every cycle thereafter. Patients had appropriate radiological imaging (CT scan, x-ray, ultrasound, MRI) to document baseline disease and response to treatment.

Patients were followed up every three weeks for hematological, hepatic, renal and cardiac toxicities. The toxicities were graded according to the Gynecologic Oncology Group common toxicity criteria grade (Appendix C). Radiological imaging was repeated after 2 cycles to assess disease status. Patients who achieved complete and partial response were re-evaluated every 4 weeks later to confirm the initial observation of response. Patients who completed at least 2 cycles were considered evaluable.

Although pegylated liposomal doxorubicin is not associated with significant nausea or vomiting, all patients were pre-medicated with a 5HT3 antagonist (anti-emetic) prior to receiving cisplatin and were properly hydrated as per local institution protocol for cisplatin infusion.

The primary endpoint was the objective response rate as determined by physical examination and radiological assessments.

Secondary endpoints included time to response, duration of response and time to progression. Safety was assessed by examination of adverse events, clinical laboratory data and vital signs. Adverse events, use of cytokines and changes in the laboratory parameters were summarized and tabulated.

Sample Size

The sample size was not calculated since this was a case series study.

Data Analysis

Descriptive statistics using mean, range and standard deviations were performed on the quantitative data. Percentages alone were calculated for qualitative data. Mean time to response, duration of response and time to progression in months were calculated.

Results

There were a total of 8 patients who received pegylated liposomal doxorubicin from 2000-2004. Three out of the 8 patients had ovarian malignancy (38%) while 5 had uterine malignancy (62%). Three of the 8 patients (37.5%) had progressive malignancy while 5 had recurrent disease (62.55%). Ages ranged from 45-66 years old with a mean of 56 years (SD $\pm$ 7.031). Five out of 8 (62.5%) are nulligravid. The parity ranged from 0-12 with a mean of 2 (SD $\pm$ 4.155). Body mass index (BMI) ranged from 18-27 with a mean of 24 (SD $\pm$ 3.412). The mean age of menarche was 14 (SD $\pm$ 2) for all cases. The mean age of onset of menopause was 49. Majority of the patients were non-smokers (87.5) and non-alcoholic beverage drinkers (87.5%). With regards to oral contraceptive pill use, 2 out of the 8 (25%) had previous intake. (Table 1).

All the cases except for one uterine malignancy underwent total hysterectomy with bilateral salpingooophorectomy, peritoneal fluid cytology with partial/infracolic omentectomy. Bilateral pelvic lymph node dissection was performed in 2 cases of ovarian and 3 cases of uterine malignancy. Fifty percent of the cases had Stage IV disease prior to treatment. Seven out of 8 (87.5%) cases had epithelial carcinomas. Postsurgical chemotherapy was given in 7 cases and one case was given adjuvant chemotherapy alone. Of the 7 cases who received

chemotherapy, 3 cases (37.5%) had concurrent radiotherapy.

All the cases had ECOG performance score of 0.

Table 1. Characteristics of gynecologic malignancy patients on pegylated liposomal doxorubicin for persistent and recurrent ovarian and uterine malignancies.

Characteristic	Patients on Caelyx Therapy (N=8)
Cancer Type, %	
Ovarian	3 (38%)
Uterine	5 (62%)
Age, years (SD ± years)	56.5 years (SD ± 7.03 years)
Gravidity, mean (SD ± years)	3 (SD ± 5)
Parity, mean (SD ± years)	2 (SD ± 4)
Body Mass Index (SD ± years)	24.25 (SD ± 3)
Onset of Menarche, mean (SD ± years)	14 (SD ± 2)
Onset of Menopause, mean (SD ± years)	49 (SD ± 6)
Smoking Status, %	
Smoker	7 (88%)
Non smoker	1 (13%)
OCP Use, %	
Previous user	6 (25%)
Non user	2 (75%)

Toxicities

Posttreatment toxicities on the hematologic, renal, hepatic and cardiac systems were noted. (Table 2).

Grade 3-4 anemia was noted in 2 out of the 8 cases (25%). Both cases presented with anemia after the third course of treatment. There were no Grade 3-4 toxicities in both the absolute neutrophilic count and the platelet count.

There was no note of change in the protein spillage and no new onset hematuria in all the cases. A Grade 4 renal toxicity was seen in one case (12.5%) whose creatinine level increased 16 times the normal value three months after the third course of treatment.

Grade 4 liver toxicity (bilirubin level > 3 x the normal value) was noted at the start of treatment of one patient. Baseline level was elevated 5 times more than the normal value and it became 16 times elevated after the third course of treatment. There were no reported Grade 3-4 toxicities on the serum AST, ALT and alkaline phosphatase.

Table 2. Frequencies of reported toxicities of patients on pegylated liposomal doxorubicin for persistent and recurrent ovarian and uterine malignancies.

Characteristic	Patients on Pegylated Liposomal Doxorubicin Therapy (N = 8)
Palmar plantar erythrodysesthesia, %	
Absent	8 (100%)
Grade 3-4 Anemia, %	
Absent	6 (75%)
Present	2 (25%)
Platelet Count, %	
Normal	8 (100%)
Grade 3-4 Bilirubin Levels, %	
Normal	7 (88%)
Increased	1 (12%)
Grade 3-4 Creatinine Level, %	
Normal	7 (88%)
Increased	1 (12%)
Grade 3 Cardiac Ischemia, %	
Absent	7 (88%)
Present	1 (12%)

There was one case who developed anteroseptal wall ischemia (Grade 3 cardiac ischemia) after the 2nd course of treatment.

There were no reported cases of palmar plantar ethrodysesthesia or alopecia. Moreover, there were no note of neuro-sensory or neuromotor changes after the treatment.

Response Rate

All the cases developed progressive disease with a mean time to progression of 2 months. The case of endometrial adenocarcinoma with squamous differentiation from an endometriotic cyst, Stage IV who received six courses of carboplatin-paclitaxel

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Appendix A

Eastern Cooperative Oncology Group (ECOG) Performance Scale

Score	Activity Level
0	Fully active; Unrestricted activities of daily living.
1	Ambulatory but restricted in strenuous activity.
2	Ambulatory but capable of self care; Unable to work; Out of bed greater than 50% of waking hours.
3	Limited self care; Confined to bed or chair 50% of waking hours; Needs special assistance.
4	Completely disabled; No self-care.
5	Dead

Recommendations

Surgery : ECOG Score 0-2
Chemotherapy : ECOG Score 0-2
Radiotherapy : No specific recommendation

Appendix B

New York State Heart Association Classification

Class I	Patients in whom angina is provoked by strenuous exertion. Patients with cardiac disease without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest.

Continuing Treatment Outcomes of Cervical Cancer Stage IB2 and Bulky IIA using Four Different Multimodality Protocols in a Tertiary Institution: A Follow -Up Study

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Objective: To compare overall survival, toxicities and complications of four multimodality regimens used in cervical cancer patients Stage IB2 and bulky IIA in our institution. **Methods**: Ninety eight women were included : 48 patients (48.9%) underwent complete radiotherapy with cisplatin (Protocol A); 18 patients (18.36%) underwent complete radiotherapy with cisplatin then extrafascial hysterectomy and bilateral salpingo-oophorectomy (Protocol B); 16 patients (16.3%) underwent external pelvic beam radiotherapy (EBRT) then radical hysterectomy, bilateral salpingo-oophorectomy and lymph node assessment (Protocol C); and 16 patients (16.3%) underwent pelvic EBRT with cisplatin then radical hysterectomy, bilateral salpingo-oophorectomy and lymph node assessment (Protocol D). **Results**: The best outcome results were seen in Protocol C and worst with Protocol A. Two year disease free rate was 88% for Protocol C, 84% for protocol B, 80% for Protocol D and 34% for Protocol A. The five year disease free rates for protocols C and D were 86% and 70%, respectively. The follow - up time for those who belong to Regimens A and B did not reach five years. The toxicities, except for renal, were not statistically significant among the groups. **Conclusion**: The best outcomes were with Protocol C followed by Protocol D. Radiation with or without cisplatin followed by surgery proved more superior than chemoradiation alone in these subsets of patients.

Key words: cervical cancer

Cervical cancer remains a major problem in developing countries. In the Philippines, cervix ranks as second to breast among the leading cancer sites in females.[2] The choice of treatment depends on multiple factors. Current options include primary chemoradiation, primary surgery with radical hysterectomy and lymphadenectomy that may be followed by tailored chemoradiation or neoadjuvant chemotherapy followed by radical hysterectomy and tailored chemoradiation. Among the stages, Stage IB2 and Stage IIA bulky cervical cancer have drawn much interest and controversy. Evidence suggests there may be improvement in pelvic control and progression free survival in select patients, when combined therapy is used. A retrospective cohort study was done in 2004 by Toral and Luna on treatment outcomes of Cervical Cancer Stage IB2 and Bulky IIA using four different multimodality protocols at the Philippine General Hospital from November 1996 to June 2003 employing external pelvic beam radiotherapy (EBRT) and intracavitary radiation concomitant with single agent Cisplatin as

Protocol A; EBRT and intracavitary radiation concomitant with single agent cisplatin followed by extrafascial hysterectomy and bilateral salpingo-oophorectomy as protocol B; EBRT followed by radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node assessment as protocol C; EBRT concomitant with single agent cisplatin followed by radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node assessment as Protocol D.[18] In this study, the best outcomes were from protocol B albeit associated with the highest hematologic toxicity and the most number of surgical morbidities. Protocol D had the next best outcome and may be considered as treatment option in areas where intracavitary radiation facilities are not available. Chemoradiation with surgery proved to be more superior than radiation with surgery only.[18]

The care of our patients has often been lacking as their tendency to seek subsequent consults in community settings had always been a factor. Thus, the tendency to the less likely use of appropriate surgery, radiotherapy, modern equipment and guided dosing schedules become a weakness and will adversely affect eventual outcome of the disease. The present investigation followed up and compared the treatment outcomes of this subset of patients of stage IB2 and bulky IIA cervical disease in our institution reported previously in 2004 and included new patients seen after three years who have completed the same treatment modalities to determine its true value in our clinical setting.

Objective

General Objective

To compare treatment outcomes in terms of overall survival, toxicities and complications of the four different multimodality regimens used in the care of cervical cancer patients stage IB2 and bulky IIA in our institution.

Specific Objectives

1. To compare the outcome in terms of overall survival of the four different multimodality regimens used in the care of cervical cancer patients stage IB2 and bulky IIA our institution observed in 2003 with its status up to 2006.
2. To compare the outcome in terms of disease-free survival of the different multimodality regimens used in the care of cervical cancer patients stage IB2 and bulky IIA our institution observed in 2003 with its status up to 2006.
3. To compare the outcome in terms of complications and toxicities of the four different multimodality regimens used in the care of cervical cancer patients stage IB2 and bulky IIA our institution observed in 2003 with its status up to 2006.

Materials and Methods

Study Design

The study used a retrospective cohort design in which the same population of patients reported by Toral and Luna in 2004 comparing the outcome of treatment modalities for stage IB2 and bulky IIA cervical cancer were followed up based on available data and overall survival status, progression free survival and toxicities. Additional patients fulfilling the original inclusion criteria were included to further exemplify the true results of these practices. Final outcome will be reported as with no evidence of disease, progressive disease, recurrence or dead of disease.

Subjects

As specified in the previous study, the patient population in this investigation has the following characteristics:

1. Histologically confirmed large cell squamous carcinoma or adenocarcinoma of the cervix with no previous treatment
2. FIGO stage IB2 (clinical lesions confined to the cervix >4cm) and bulky IIA (clinical lesions > 4cm and extend beyond the cervix to involve the vagina but not up to the lower third without obvious parametrial involvement).

3. Eastern Cooperative Oncology Group (ECOG) performance score of 0-2 (table 7), good hematologic, hepatic, renal and cardiopulmonary function fit to undergo the radiation treatment, chemotherapy and the definitive surgery if applicable.
4. Patients who have completed either of the four treatment protocols at the institution from November 1996 to June 2003.
   Protocol A: external pelvic beam radiotherapy and intracavitary radiation concomitant with single agent Cisplatin
   Protocol B: external pelvic beam radiation and intracavitary radiation concomitant with single agent cisplatin followed by extrafascial hysterectomy and bilateral salpingo-oophorectomy
   Protocol C: external pelvic beam radiation followed by radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node assessment
   Protocol D: external pelvic beam radiation concomitant with single agent cisplatin followed by radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node assessment
5. Patients with the same characteristics as above who have completed treatment using aforestated regimens from June 2003 to June 2006.

Treatment

1. **Chemotherapy.** Chemotherapy consisted of cisplatin administered weekly at a dose of 40 mg/m^2 intravenously with a total single dose of up to 70 mg, given in a two-hour infusion with appropriate hydration. Antiemetic therapy was routinely given on the day of chemotherapy. The treatment schedule included the first administration of cisplatin within the first five fractions of radiotherapy. Renal (serum creatinine level and electrolytes) and liver functions, hemoglobin, white blood cell counts and platelet counts were assayed before each cisplatin administration. Chemotherapy was given provided the leukocyte or granulocyte count was $>4 \times 10^9$/L and 1.5×10^9/L, respectively, and the platelet count was $>100 \times 10^9$/L, hemoglobin > 110 G/L, creatinine within normal limits and transaminases within and up to three times the normal upper limit. Otherwise, cisplatin delivery was postponed until hematologic recovery was achieved. Colony-stimulating growth factors were used as necessary. In certain cases where the creatinine clearance decreased to 30-60ml/min, chemotherapy was given at a reduced dose (by 50%), and deferred if creatinine clearance is 30 ml/min. Electrolyte imbalances were treated accordingly. Where more than one type of toxicity is reported in a category (hematologic, renal, gastrointestinal and hepatic), the most frequent and higher grading is recorded. Chemotherapy was given to patients who belong to Protocols A, B and D.

2. **Radiotherapy.** Patients received external beam radiotherapy using Co60 to the whole pelvis for a total dose of up to 50 Gy (in 180-200 cGy fractions). Patients were treated with the four-field box technique. The irradiated volume was to include the whole uterus, the paracervical, parametrial, and uterosacral regions, and the external iliac, hypogastric, and obturator lymph nodes. The minimal margins were the upper margin of L5 (superiorly), midportion of the obturator foramen or the lowest disease extension (inferiorly), and 1 cm beyond the lateral margins of the bony pelvis and its widest plane (laterally). For the lateral fields, the anterior margin was the anterior edge of the pubic symphysis or 3 cm in front of the sacral promontory. The posterior margin was the S2-S3 interspace. External pelvic beam radiotherapy was given to all patients in this study.

   Low-dose brachytherapy was performed in one intracavitary application after the completion of pelvic radiotherapy. Standard Fletcher–Suit applicators were used. The dose to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 30 - 40Gy, for a cumulative dose of 80-90 Gy, and the cumulative dose to point B (the pelvic wall) was 55 Gy. Low dose brachytherapy was given in all

patients who belong to Treatment Regimens A and B.

3. **Surgery.** The patients in Protocol B underwent Extrafascial hysterectomy which included resection of the uterus outside the plane of the pubovesical fascia along with its attached parametrial soft tissue and a margin of the upper vagina, with bilateral salpingo-oophorectomy. Radical hysterectomy among patients in Protocols C and D was carried out by obtaining wider parametriae, dissection of the ureter down to its bladder attachment, clamping and ligating the ligaments from their pelvic insertion and taking out 3-4 cm of the proximal vagina. For patients in Protocols B, C and D, pelvic and para-aortic lymph node assessment was done by palpation of the course of the pelvic and para-aortic lymph node chains from the level of the circumflex iliac vessels inferiorly and cephalad to the level of the inferior mesenteric artery.

Follow – up

Patients who were included in this study continued to be seen in the Out Patient Clinic. They were followed up every month during the first year, every 2 months during the second year and so on, and may be altered depending on their clinical outcome. Patient assessment was done in the form of history taking, general physical examination and pelvic examination, Papanicolau smears, chest x-rays, transvaginal ultrasound, including blood examinations whenever necessary.

Primary outcome measures are in the form of overall and progression-free survival, and secondary outcomes were toxicities and complications. Progression-free interval is calculated in months from the initial date of treatment to the date of the first physical or radiographic evidence of disease progression, death or the last follow-up visit. Overall survival is expressed in months from the initial date of treatment to the date of death or the last follow-up visit. Toxicities were noted and described starting from date of first day of treatment according to the Gynecologic Oncology Group Common Toxicity Criteria Grade (October 1988). Disease progression, persistence or recurrence and death were described as to time of detection in months from the last day of treatment. All interventions and present status including complications after such interferences were noted and reported.

Statistical Analysis

Tables showing the absolute values and percentage of the results are demonstrated and the calculated means for each clinical characteristics were cited with corresponding range, as necessary. Clinical associations or relationships were computed using Chi-square for histologic type, stage of the disease, tumor size and eventual toxicities. Analysis of Variance was used to assess the influence of chemotherapy cycles, radiation dose and length of treatment. A level of significance of 0.05 was assigned and p values less than 0.05 were considered significant. For the long term outcome of the previous set of patients and the overall outcome for the entire population, chi-square test was used and the disease free interval calculated using log rank test with confidence interval (CI) at 95%. Likewise, a level of significance of 0.05 was assigned and p values less than 0.05 were considered significant. Best outcome is expressed as the number or proportion of patients who manifest with no evidence of disease following treatment.

Results

Demographic Data (Tables 1 and 2).

A total of 98 cases were reviewed. The previous report of Toral and Luna included 70 patients. Additional 28 cases met the criteria for inclusion to this study from the year 2003 to 2006. From the preceding report, 26 patients completed protocol A (26.5%), 12 patients had protocol B (12.2%), 16 patients had protocol C (16.3%), and 16 had protocol D (16.3%). In this study, 48 patients completed protocol A (48.9%), 18 patients completed protocol B (18.36%), and the same patients were in protocols C (16 patients, 16%) and D (16 patients, 16%). Demographic data are presented in table 1. The youngest among the patients was 25 years old, while

Table 4. Incidence of toxicities in each treatment group (N=98).

	Protocol A (n=48)	Protocol B (n=18)	Protocol C (n=16)	Protocol D (n=16)	p value**
Kidney Toxicity					
None	16 (33.3)	6 (33.3)	4 (36.4)	9 (56.3)	
Grade 1	11 (22.9)	3 (16.7)	3 (27.3)	5 (31.3)	
Grade 2	20 (41.7)	9 (50.0)	1 (9.1)	2 (12.5)	
Grade 3	1 (2.1)	—	3 (27.3)	—	0.004
Liver Toxicity					
None	32 (66.7)	13 (72.2)	7 (70.0)	12 (75.0)	
Grade 1	13 (27.1)	5 (27.8)	3 (30.0)	3 (18.8)	
Grade 2	3 (6.3)	—	—	1 (6.3)	0.888
Gastrointestinal Toxicity					
None	38 (79.2)	13 (72.2)	8 (88.9)	15 (93.8)	
Grade 1	7 (14.6)	—	—	1 (6.3)	
Grade 2	2 (4.2)	2 (11.1)	1 (11.1)	—	
Grade 3	—	1 (5.6)	—	—	
Grade 4	1 (2.1)	2 (11.1)	—	—	0.195
Hematologic Toxicity					
None	5 (10.4)	4 (22.2)	4 (30.8)	2 (12.5)	
Grade 1	18 (37.5)	3 (16.7)	7 (53.8)	4 (25.0)	
Grade 2	20 (41.7)	10 (55.6)	2 (15.4)	10 (62.5)	
Grade 3	5 (10.4)	1 (5.6)	—	—	0.110

** Chi square

Table 5. Overall clinical outcomes in each treatment group (N= 98).

	Protocol A (n=48)	Protocol B (n=18)	Protocol C (n=16)	Protocol D (n=16)	p value
Outcomes					
No disease	26 (54.2)	13 (72.2)	14 (87.5)	12 (75.0)	
Persistent	1 (2.1)	1 (5.6)	—	—	
Progressive	18 (37.5)	2 (11.1)	2 (12.5)	1 (6.3)	
Recurrence	—	1 (5.6)	—	2 (12.5)	
Death	3 (6.3)	1 (5.6)	—	1 (6.3)	0.022**
Disease Free Duration (95% CI)	20 (13, 26)	40 (29, 51)	83 (67, 100)	80 (58, 101)	0.002***
Mean duration of follow - up (months)	12.35	23.5	44.9	39.6	

** Chi square
*** Log rank test

Table 6. Long-term clinical outcomes in each treatment group (N = 70).

	Protocol A (n=48)	Protocol B (n=18)	Protocol C (n=16)	Protocol D (n=16)	p value
Outcomes					
No disease	10 (38.5)	9 (75.0)	14 (87.5)	12 (75.0)	
Persistent	—	—	—	—	
Progressive	13 (50.0)	2 (16.7)	2 (12.5)	1 (6.3)	
Recurrence	—	—	—	2 (12.5)	
Death	3 (11.5)	1 (8.3)	—	1 (6.3)	0.006**
Categorized Outcomes					
Favorable	10 (38.5)	9 (75.0)	14 (87.5)	12 (75.0)	
Unfavorable	16 (61.5)	3 (25.0)	2 (12.5)	4 (25.0)	0.005**
Disease Free Duration (95% CI)	17 (10, 24)	43 (30, 55)	83 (67, 100)	80 (58, 101)	0.001***

** Chi square
*** Log rank test

No other patients were added to Protocols C and D for 2003-2006. For Protocol C, the mean duration of follow-up was 44.9 months. The range was 3-97 months. Fourteen patients (87.5%) had no evidence of disease while two patients had progressive disease (12.5%) and were for chemotherapy.

For protocol D, the mean duration of follow-up was 39.6 months. The range was at 4-104 months. Twelve patients had no evidence of disease (75%) while one patient had disease progression (6.3%). Two of the patients had recurrence (12.5%) manifested as a para-aortic mass, and inhomogenous masses over the pelvic and paravertebral areas on CT scan. These patients were for chemotherapy and for referral to hospice care. One patient died of disease (6.3%).

Follow-up after three years of the previous group of patients (N=70, Table 6), the best outcome, measured as with no evidence of disease, was seen with protocol C (87.5%) followed by protocols B (75%) and D (75%). Protocol A had the poorest outcome (38.5%). Statistical analysis showed significant difference over categorized outcomes among the groups (p value 0.006). The mean disease free duration for protocol C was 83 months (95% CI, 67-100). Protocol D followed at a duration of 80 months (95% CI, 58-101) and protocol B at 43 months (95% CI, 30-55). Disease free duration with protocol A was only 17 months (95% CI, 10-24). These results were statistically significant (p value 0.001). This set of patients in the initial report showed that best outcome was with protocol B in 83%, followed by protocol D in 81%. Worst outcome was with protocol A (46.2%). Using Kaplan Meier Analysis (Figure 2), the two year disease free rate was 32% for protocol A (95% CI), with best values observed among the surgical groups. The highest was at 87% for protocol C (95% CI), 82% for protocol B (95% CI), and 80% for protocol D (95% CI). Overall survival showed statistically significant difference between the 4 arms (p = 0.002). Using the same analysis, the five year survival rates for protocols C and D were 87% and 69%, respectively (95% CI). There was stable value for disease free rate for regimen C and 11% drop in disease free rate for regimen D after 3 years. The follow – up time for those who belonged to regimens A and B did not reach 5 years.

The overall outcome (N=98), presented in Table 5 inclusive of the 28 additional patients from 2003-2006 showed best outcome results for protocol C (87.5%), followed by protocol D at 75%. Protocol B closely followed at 72.2%. Worst outcome was still with protocol A at 54.2%. Statistical analysis showed significant difference among the outcomes (no

evidence of disease, persistence, progression, recurrence and death (p value 0.022). The mean disease free duration for protocol C was 83 months (95% CI, 67-100). Protocol D followed at mean disease free duration of 80 months (95% CI, 58-101), with a big drop to 40 months with protocol B (95% CI, 29-51) and to 20 months for protocol A (95% CI, 13-26). The differences in the disease free survival for patients in these four arms showed statistical significance (p value =0.002). Using Kaplan Meier Analysis (Figure I), the two year disease free rate was 34% for protocol A, the better values were observed among the surgical groups which was highest at 88% for protocol C, followed with the 84% for protocol B, and 80% for protocol D. Overall survival showed statistically significant difference for all arms (p = 0.002). Using the same analysis, the five-year disease free rates for protocols C and D were 86 and 70%, respectively (95% CI). From this analysis, protocol C decreased by 2% while protocol D decreased by 10% from the previous rate observed. The follow – up time for those who belonged to regimens A and B did not reach five years.

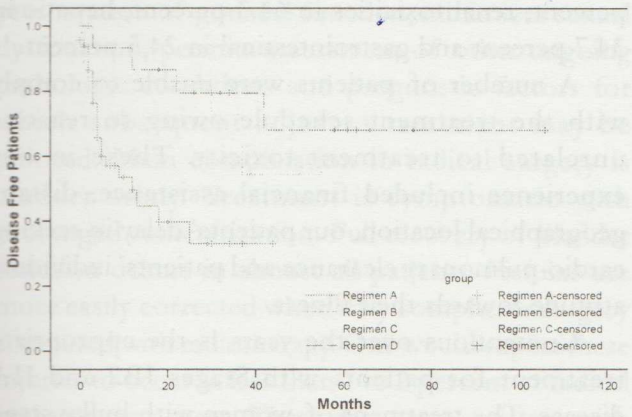

Figure 1. Overall Kaplan Meier estimates of disease free survival among patients assigned to receive the four different treatment modalities from 1996 - 2006 (N = 98).

Discussion

Based from the results of the previous study, the best outcomes are from protocol B, albeit associated with the highest hematologic toxicity and the most number of surgical morbidities. Protocol D had the next best outcome and may be considered as a good treatment option especially in areas where intracavitary radiation facilities are not available. Chemoradiation with surgery proved to be more superior than radiation with surgery only. Consistent with the above findings are best outcomes with surgery following radiotherapy in this study. Unlike the end results of the above study, the best outcome in this investigation is with protocol C followed by protocol D. This is expressed as two year disease free rate of 88% for protocol C (95% CI), 84% for protocol B (95% CI), and 80% for protocol D (95% CI). For protocol A, it is 34% (95% CI). Furthermore, the five-year disease free rates for protocols C and D were 86 and 70%, respectively (95% CI). The follow–up time for those who belong to regimens A and B did not reach five years.

Although cervical cytology screening programs have steadily decreased the incidence of cervical cancer in developed countries, cervical cancer remains a major problem in developing ones. Approximately 471,000 women are diagnosed annually with cervical cancer and 234,000 women die of this disease.[1] The 2005 Philippine Cancer Facts and Estimates states that cervix ranks as the 5th leading cancer site overall for both sexes combined and second to breast among females alone.[2] In the Philippines, the median survival is 76 months and the five year survival rate is 51.7% and ten year survival rate of 44.54%.[2] In our institution, a total of 4294 consults for cervical cancer were made in 2005 or about 62% of gynecologic malignancies, the lowest in the past decade. There were 512 new patients (58%), and this stable number of new cases throughout the years is an indirect testimony to the failure or even absence of effective screening program in the country.

The choice of treatment depends on the stage of the tumor. For the smaller tumors confined to the cervix (FIGO stages IA and IB1), treatment consists of surgery or radiotherapy, with 5-year survival rates of 80% to 95%.[3] Patients with Stage IA1 disease are effectively treated with extrafascial hysterectomy while patients with Stage IA2 and IB1

disease are treated with radical hysterectomy and lymphadenectomy. Primary chemoradiation is considered the standard of care for patients with advanced disease (FIGO Stage IIB–IVA). For the more advanced disease, the 5-year survival is less favorable, with radiotherapy as the sole modality. Many attempts have been made over the last decades to improve the treatment outcome in this group. The tolerance of the normal tissues in the pelvis is a major barrier for radiotherapy and combinations of chemo- and radiotherapy were subsequently studied. Chemotherapeutic agents given before (induction), concomitantly, or after (adjuvant) radiotherapy have been integrated into treatment protocols. Of those, the concomitant approach has drawn the most enthusiasm. The governing principles for concurrent chemotherapy and radiotherapy include the potential of cytotoxic agents to increase tumor cell kill, inhibit repair of radiation damage, induce cell synchronization, recruit non-proliferating cells into the cell cycle, and the sensitization of hypoxic cells. The superiority of concurrent cisplatin-based chemotherapy and radiotherapy over radiotherapy alone in invasive cervical cancer has been shown in five randomized trials. The 3-year survival rates were increased from 40 percent to 69 percent in stage III and IV tumors.[3] Significant reduction in the distant relapse rate (14% *vs* 33%) was observed in patients treated with pelvic radiation plus concurrent cisplatin and fluorouracil, compared with the control group treated with pelvic and para-aortic radiation.[4] Another large-scale phase III trial of locally advanced cervical carcinomas also showed that radiation plus concurrent cisplatin-based chemotherapy consisting of either weekly cisplatin or a combination of cisplatin, fluorouracil and hydroxyurea resulted in a lower frequency of lung metastasis (3% and 4%, respectively, vs 10%) than radiation plus concurrent hydroxyurea.[5] Moreover, in these two studies, reductions in local recurrence rates of 37 percent and 46 percent were noted in patients who received concurrent cisplatin as compared with those who did not. The decrease in both local and distant relapses resulted in significantly higher rates of progression-free and overall survival in the groups treated with concurrent cisplatin than in those treated without.[6] These positive findings led us to introduce weekly cisplatin as a standard component of treatment since May 1999, and into our institution in the same year. It is unclear if the observed reduction in the rate of distant recurrence is a consequence of improved local control or if cisplatin has a direct cytotoxic effect. Since the doses of concurrent chemotherapy utilized in these studies are far less than those usually given for the treatment of solid tumors, the effect of the chemotherapy on micrometastatic disease is questionable.[7] The local study done by Toral and Luna followed up by this research showed the superiority of admixing chemotherapy with radiation, consistent with international studies.

The main toxicity encountered during combined chemoradiation is hematologic and gastrointestinal. These, fortunately are easy to treat. The previous report stated that hematologic toxicity occurred in 81.4 percent of the population, followed by renal in 60 percent and then toxicities in the hepatic and gastrointestinal system. Except for the hematologic toxicities, comparing each of the groups showed no statistical significance. These findings were consistent with this study, although only renal toxicities gained significant statistical difference ($p=0.004$). Hematologic toxicities occurred in 84.7 percent, renal toxicities in 64.3 percent, hepatic in 34.7 percent and gastrointestinal in 24.5 percent.

A number of patients were unable to comply with the treatment schedule owing to reasons unrelated to treatment toxicity. These in our experience included financial assistance, distant geographical location, our patients' delay in seeking cardio-pulmonary clearance and patients' individual attitude towards their illness.

Contentious over the years is the appropriate treatment for patients with Stages IB2 and IIA disease. The treatment of women with bulky stage IB cervical cancers has historically been only partially satisfactory, with survival rates of 70 to 75 percent, substantially below the rates of 88 to 92 percent expected with smaller stage IB cancers.[8] For stage IB–IIA patients with tumor diameter 3 cm or greater, the 5-year survival rate is reported to be 31–66 percent after surgery or radiotherapy. For each 1-cm increase in cervical diameter (3-9 cm), there was a nearly 3-fold increase in the risk of recurrence.[9]

The most common size of in our study is in the [illegible] category, seen in 36 percent of the population. Majority of these larger tumors are seen in protocol B, suggesting that the possible worst outcome could have been affected by size. However, the final statistical analysis showed no significant difference in terms of tumor size. Initial surgery in patients with bulky cervical cancer is difficult because of complexity in performing appropriate parametrial dissection and vaginal resection of the bulky mass.[6] High pelvic lymph node metastases in 35.2 to 80 percent has been documented.[10] Current options for this subset of patients include primary surgery with radical hysterectomy and lymphadenectomy followed by tailored chemoradiation, primary chemoradiation or neoadjuvant chemotherapy followed by radical hysterectomy and tailored chemoradiation.[1] Higher complication rates (40%) are experienced when patients receive both radical surgery and radiation therapy compared to primary chemoradiation alone (25%).[1] Surgical morbidities encountered in these two local studies reported only four morbidities: two cases of bladder injuries and a case of re-exploration for ligation of bleeders from Protocol A and a rectal injury in Protocol D. No additional morbidities were observed after three years. Radical surgery allows preservation of gonadal function, minimizes sexual dysfunction, permits assessment of other ongoing pathologic conditions and prognostic factors for which subsequent adjuvant treatment may be tailored. Main complication in radical surgery is bladder atony. Treatment is symptomatic with prolonged catheterization. Full recovery of bladder function occurs in almost all patients. Fistulae are more easily corrected when they complicate surgery compared with radiotherapy. One would expect these injuries to occur in less than 1 to 2 percent of radical hysterectomy cases. These data are consistent with our local experience. On the other hand, radiotherapy is an option for all stages and for patients who are not good surgical candidates by virtue of co-morbidities of age, weight and concurrent diseases.[11] In 1997, Landoni, et al. performed a phase III randomized study in which patients with stages IB and IIA cervical cancer were randomized to receive both external irradiation and brachytherapy versus a radical hysterectomy and lymph node dissection.[13] The final results of the study demonstrated that there was no statistically significant difference in overall and disease-free survival rates for the two treatment groups. Overall survival rate was 83% for each group. Disease-free survival rates were also similar for the two groups at 5 years: 74% for surgery and 74% for irradiation. Although the survivals were the same for the two treatment modalities, more than 60 percent of the patients who were initially treated with radical hysterectomy and lymph node dissection also received postoperative pelvic irradiation. For the newer studies, a retrospective analysis of survival statistics for 446 women with stage IB cervical cancer treated primarily with radiotherapy or surgery over a period of 31 years at the University of Michigan Medical Center. Although they did not separate patients into groups based on prognostic indicators such as tumor size or volume, there was no difference in the 5-year survival for women treated by radical hysterectomy and pelvic lymphadenectomy compared with those treated with traditional radiotherapy.[12] Multiple Variate Analyses controlling for tumor size (4 cm or smaller compared with larger than 4 cm) found equivalent overall survival rates for the two treatment groups.[12] Among the women with larger cancers there was no significant difference in 5-year survival between the groups.[12] Despite the consistency between these trials and many other similar studies, the treatment results from the Surveillance, Epidemiology and End Results database did not confirm that surgery and radiotherapy are equally effective treatment modalities for women with stage IB or IIA cervical cancer.[12] In an intent to treat analysis by Brewster, after controlling for age and tumor size within the cohort of women with smaller tumors, there was a significant 5-year survival advantage for those treated surgically.[12] Even within the type of radical hysterectomy (type II vs type III), there is controversy regarding the equivalency of these procedures for those with early stage cervical cancer.[13] One recent study by Landoni, et al. showed equivalency for those patients with stage IB-IIA cervical cancer for the type II versus type III radical hysterectomy; however, this study is underpowered to adequately examine issues of equivalency and

Some authors believed that after cisplatin, the residual tumor is insensitive to subsequent irradiation.[6] They proposed that the drug induces radioresistance in tumor cells, or this observation may be explained by tumor cells that survive after cisplatin with an inherent resistance to radiation. Hence, they proposed that once neoadjuvant chemotherapy is applied, a definite surgical approach to radically remove the cervical residual tumor should be undertaken. On the contrary, women with previously untreated bulky (primary tumor > 4 cm) stage IB or IIA non–small-cell carcinoma of the uterine cervix were randomly assigned to receive either cisplatin , vincristine and bleomycin for three cycles followed by radical hysterectomy (neoadjuvant chemotherapy arm) or receive primary pelvic radiotherapy only (radiotherapy arm).[6] No routine hysterectomy was applied to the control group, and only six patients (12%) had residual tumors after radiotherapy and had to undergo radical hysterectomy. Thirty-one percent of patients in the neoadjuvant chemotherapy arm and 27 percent in the radiotherapy arm had relapse or persistent disease after treatment, and 21 percent in each group died of disease. Estimated cumulative survival rates at 2 years were 81% for the neoadjuvant chemotherapy arm and 84% for the radiotherapy arm, the 5-year rates were 70% and 61%, respectively.[6] On statistical analysis, there were no significant differences in disease-free survival and overall survival.[6] In the GOG study, hysterectomy was part of the scheduled treatment for all patients. With similar follow-up periods, 79 percent of the patients in the radiotherapy arm of this study were still alive,[6] whereas in the GOG study, 74 percent of the patients treated with radiotherapy followed by hysterectomy remained alive. Therefore, the value of hysterectomy again in patients who have received an optimal regimen of radiotherapy became doubtful. They believed it is only appropriate as a salvage therapy and that it should be undertaken with a more radical approach than an extrafascial hysterectomy.[6] Although neoadjuvant chemotherapy effectively reduces the primary tumor volume, 9 percent of the patients in the neoadjuvant chemotherapy arm had distant relapse. This is only slightly lower than the 12 percent of patients with distant relapse in the radiotherapy arm.[6] Twenty–one percent of the patients in the neoadjuvant chemotherapy arm and 12 percent in the radiotherapy arm had local relapse. These things however are still in its infancy in our institution, primarily because the cost of treatment had been a perennial factor affecting our experiences.

The present investigation followed up and compared the treatment outcomes of these previously evaluated patients and included new patients seen from April 2003 to June 2006 who have completed the same modalities. The objective was to determine the true value of these treatment options in terms of overall survival, toxicities and complications. It is of great advantage that we were able to come up with a comparison employing four modalities measuring up with global studies. The study is a longer follow-up of the survival states of these patients after three years from the previous report that defined strength to these treatment strategies. Best outcome in terms of survival is with pelvic radiation followed by surgery, with or without a radiosensitizer. Delays in treatment have always influenced these outcomes as this had been comparably significant among these modalities. We could surmise therefore, that although in international literature treatment concurrent with cisplatin have shown survival benefits, this simultaneous giving out of chemotherapy may have been governed by factors inherent to us such as financial incapabilities, medical co-morbidities, toxicities with chemotherapy, and patient attitudes toward chemotherapy causing delay and altered compliance prolonging treatment time. This is the factor that made Protocol C distinct from the rest. Delivery of radiation also during the period these treatments were utilized is a huge limitation, especially with intracavitary radiation. Most of our patients would crowd to and seek treatment in only two institutions. In coming up with a better recommendation, it would be of much significance if in this study we have added more patients in Protocols C and D to further strengthen our results. In our local setting therefore, it would be essential to consider economic status and accessibility of facilities in coming up with a treatment regimen to use that would best benefit our patients, and that

our unfortunate situation should never supersede sound clinical judgment. A randomized controlled trial would be able to address what may be the most appropriate modality in our locale, and simultaneous investigation in multiple centers in our country. It would be noteworthy to emphasize the importance of quality of life as an outcome, that state of complete physical, mental and social well being in cancer survivors - if they believe to have resumed their full premorbid potentials and level of activity, freedom from the anxiety of agony and death, opportunity to go back and attend to their valued ones, as psychological as well as physical problems were highly correlated with a person's stance and acceptance of his own condition.

We have struggled to deliver quality medical attention to our patients but it is not always without confounding factors that preclude realization of our best interests. It is in these situations where our ingenuity is brought forth, all in the hope of giving the best treatment that our patients deserve.

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Primary Rectal Adenocarcinoma with Vulvar Extension in a Young Multigravid: A Diagnostic and Therapeutic Dilemma

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Cancer in association with pregnancy is a rare and an unfortunate coexistence. A 40- year old G7P5 (4114) was diagnosed to have rectal adenocarcinoma extending to the vulva at 24 weeks age of gestation. Further complicated by hospital-acquired Pseudomonas infection, the contemplated administration of neoadjuvant chemotherapy was withheld. Due to oligohydramnios and preterm labor, cesarean section was performed at 32 weeks age of gestation. She delivered to a live pre-term baby boy weighing 1.6 kg with a Ballard score of 32 weeks. Four weeks post-partum, definitive surgical procedures were done consisting of radical vulvectomy, abdomino- perineal resection, posterior vaginectomy, tumor resection and bilateral groin node dissection. This is a classical case where multidisciplinary team approach is crucial to optimal delivery of health care to both mother and baby. The team included a perinatologist-obstetrician, gynecologic oncologist, neonatologist, colorectal surgeon and infectious disease specialist.

Key words: adenocarcinoma, rectal cancer, vulvar cancer

Cancer and pregnancy is a rare coexistence. The reported incidence ranges from 0.07% to 0.1% for all malignant tumors.[1] Pavlidis reported that the most common malignant tumors complicating pregnancy are those most frequently seen in the reproductive age which includes breast cancer, cervical cancer, Hodgkin's disease, malignant melanoma, leukemia, ovarian cancer and colorectal cancer.

Pregnancy-associated malignancies present significant challenges as a result of the conflict between optimal maternal therapy and fetal well-being. The diagnosis of a malignancy during such delicate state of womanhood is indeed a traumatic experience with tremendous impact on the patient and her family. The emotional impact on the mother concerning her health and that of her fetus creates a complex management problem that necessitates a multi-disciplinary treatment plan. It is therefore the responsibility of the health care provider to present the available management options and discuss their benefits and potential risks.

Objectives

This paper is aimed at the following objectives:

1. To present a case of a primary rectal adenocarcinoma extending to the vulva in a young 40-year old multigravida.

2. To discuss the pathophysiology of the tumor in this young patient.
3. To discuss the dilemma in its diagnosis and treatment.
4. To highlight ethical issues involved and the importance of multi-disciplinary team-approach in its management.

The Case

A forty-year old G7P5 (4114), C.B. noted an enlarging perineal mass 7 months prior to admission, described as firm, non-tender, about the size of a kernel. This was accompanied by decreased caliber of stools and pain during defecation. These symptoms were ignored and no consultation was made.

A month later, the mass increased to about 1 cm x 1 cm, this time, associated with tenderness and yellowish foul-smelling discharge. At a provincial hospital, Pap smear revealed normal result. Biopsy of the mass was advised but she declined. Having been amenorrheic for 5 months with a notably enlarging abdomen, she presumed she was pregnant when she felt quickening at around this time. No test was undertaken nor consultation done.

Two weeks PTA (at 22 weeks AOG), an obstetrician was consulted who requested for a pelvic ultrasound which revealed an 18 weeks and 6 days fetus. The vulvar mass was examined and was felt to be seemingly an extension of a larger intraluminal rectal tumor located at the anterior rectal wall traversing the rectovaginal septum. Referral to a surgeon was made and biopsy of both rectal and vulvar lesions was done. Histopathology revealed tubular adenoma (Rectum) and papillary adenocarcinoma (Vulva). Subsequent referral to this institution was done.

Upon admission (at 24 weeks AOG), patient was in threatened pre-term labor. The genitalia showed a 3 cm x 3 cm nodular fungating and partly ulcerated mass located at the inferior half of the left labium minus (Figure 1). Internal examination revealed a soft, closed, smooth cervix; the corpus was enlarged to 5 months size with no adnexal mass or tenderness. Recto-vaginal examination, however, indicated that the vulvar mass was continuous with a bigger intraluminal rectal mass which occupied the middle third of the rectovaginal septum with an approximate tumor volume of 4.5 cm x 4.0 cm x 2.0 cm. Repeat biopsy of this mass revealed adenocarcinoma.

Figure 1. Vulvar mass on admission.

The past medical, family, reproductive, personal and social histories as well as the systems review were all non-contributory.

She was promptly placed on intravenous tocolysis and steroid on admission. Co-management with the Sections of Perinatology, Neonatology, Gynecologic Oncology and Colorectal Surgery was decided upon. Following extensive counseling, the couple decided to prioritize the health interest of the mother and to proceed immediately with the definitive surgical management if needed.

After consultation with the Ethics Committee, she was worked-up for surgery. Tocolysis was discontinued and the team waited for spontaneous vaginal delivery. During this period, the Gynecologic Oncology Service suggested a neo-adjuvant chemotherapy. However, the patient developed systemic Pseudomonas infection, hence, chemotherapy was deferred. Infectious disease service recommended antibiotic therapy with Ceftazidime 1 gm IV q 8 hrs for 2 weeks. The fever lysed after three days of antibiotic treatment. In the interim, the Perinatology Service suggested fetal surveillance with sonography every two weeks. Serial

fetal monitoring showed normal growth development.

During her hospital stay, the vulvar and rectal masses were noted to be enlarging (Figure 2). Patient was managed medically and prepared for surgery.

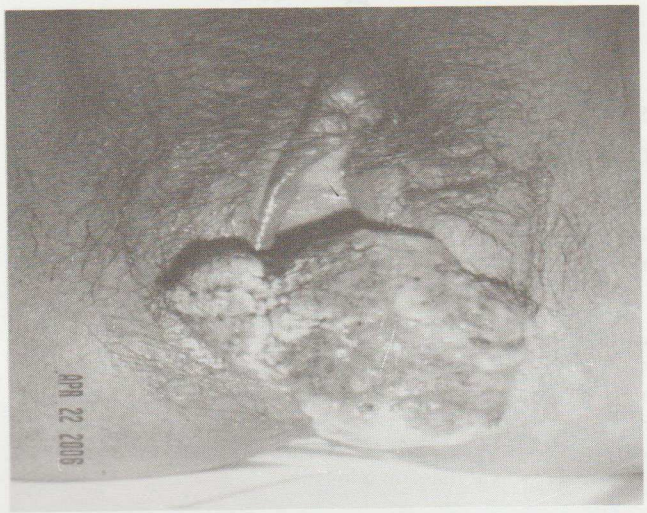

Figure 2. Vulvar mass, 6 weeks upon admission.

At 32 weeks age of gestation, when ultrasound showed an AFI of 3.4 cm and EFW of 1.9 kg, the Perinatology Service recommended termination of pregnancy. She delivered by cesarean section to a live preterm baby boy with Apgar score of 8, 9, Ballard Score of 32 weeks and a birth weight of 1.6 kg, appropriate for gestation (AGA).

Four weeks post-partum, after correction of hypoalbuminemia and hypokalemia, definitive surgery with Abdominal-perineal Resection, Posterior Vaginectomy, Radical Vulvectomy and Bilateral Groin Node Dissection was done (Figures 3-9). Intra-operatively, the exophytic rectal mass measured 6.0 cm x 4.0 cm which extended into the serosal surface and out to the vulva (Figures 11-12). No gross finding suggestive of abdominal tumor extension was noted. Histopathology showed adenocarcinoma, well-differentiated, rectum with involvement up to the serosa, perineum and rectovaginal septum (Figures 13-16). The patient was staged as IIB (T4NoMx) and the plan of the service was to give adjuvant chemotherapy with 5-FU and Leucovorin.

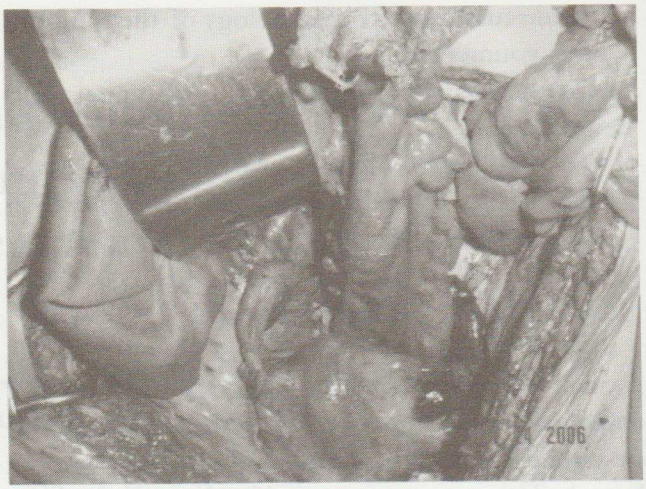

Figure 3. Abdominal resection (prior to colostomy).

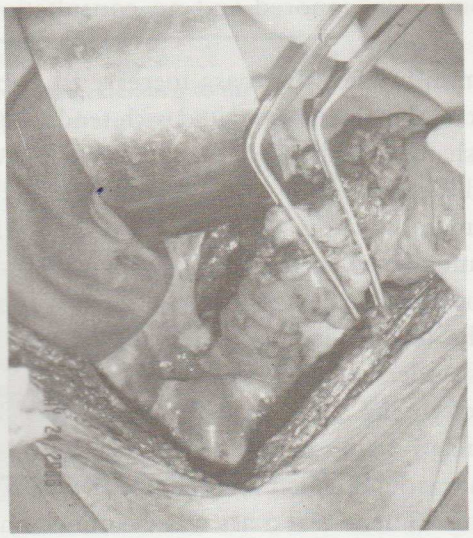

Figure 4. Colostomy procedure.

Figure 5. Post-hysterectomy.

malignant neoplasms in pregnant women. But as the trend for delaying pregnancy into later reproductive age becomes more common, physicians can probably expect to see more cases of cancer in association with pregnancy as maternal age is the one of the most powerful predictors of cancer risk.

To establish the primary neoplasm in C.B.'s case was the first dilemma encountered. She presented with rectal and vulvar masses which both showed adenocarcinoma on histopathology.

The peak age incidence of malignancies does not coincide with the peak reproductive years. In the order of decreasing frequency, cervical cancer is the most common to co-exist with pregnancy (0.24% - 0.45% per 1,000 pregnancies) and vulvar cancer is the sixth with an incidence of 0.005 per 1,000 pregnancies[2]. Colorectal cancer on the other hand, has an incidence of 1 per 13,000 deliveries.[3]

Cancer of the vulva is primarily a disease of women in the sixth and seventh decades of life, although it can occur in less than age 40 in 15 percent[3] of cases. C.B. at 40 belongs to the exception. To be considered primary, there must be no other suspicious tumor in the adjacent areas like the cervix, vagina, urethra or rectum. When rectovaginal examination revealed a large intraluminal rectal lesion, vulvar cancer was least likely to be the primary.

Considering the location and the biopsy result, primary Bartholins' gland adenocarcinoma was also considered. This accounts for approximately 5 percent of vulvar malignancies with the most common histologic type being adenocarcinoma (40%).[12] Its diagnosis, however, needs to satisfy the Honan's criteria, namely 1) the tumor is in the correct anatomic position, 2) it is located deep in the labium majus, 3) the overlying skin is intact, and 4) there are some recognizable normal glands present.[12] Strict adherence to the criteria results in under-diagnosis such that transition between normal and malignant tissue is the best criterion. This was not demonstrated upon review of the biopsy slide of our patient.

Colorectal cancer is highest at age 60 - 70 years although less than 20 percent of cases may occur before the age of 50[18] and only 8 percent occurs before age 40[19], to which our patients belong. The pathophysiology of colorectal cancer is not fully understood. Factors associated with the development of colorectal cancer include family history of colorectal cancer, polyps in the colon and rectum and inflammatory bowel diseases. When colorectal carcinoma is found in a young person, pre-existing ulcerative colitis or one of the polyposis syndromes must be suspected. The polyposis syndrome accounts for 3 percent to 5 percent of all colon cancers. The mutations in one of several mismatch or pair genes are known to be responsible in this syndrome. The genes are transmitted in an autosomal dominant pattern, thus, individuals have a 50 percent chance of passing the condition to their children. However, C.B. denies having any of the mentioned risk factors.

Colorectal cancer may present as abdominal or rectal pain, anemia, rectal bleeding and change in bowel movement. This patient presented with decreased stool caliber and pain on defecation. Considering the symptoms presented by the patient and the size of the rectal tumor and its continuity with the vulvar mass, primary rectal adenocarcinoma with metastases to the vulva became the prime consideration. No report so far has defined a set of criteria to differentiate primary vulvar from primary rectal carcinoma. Likewise, review of literature did not reveal reports of colorectal cancers extending to the vulva.

Colorectal cancer in pregnancy is an extremely rare condition with a reported incidence of 0.002 percent. Around 275 cases of this malignancy associated in pregnancy have been reported in the literature. Woods, et al. report an incidence of 1 in 13,000 deliveries[11]. The symptoms include nausea, vomiting, abdominal pain, altered bowel movements and rectal bleeding. These symptoms are commonly found in the pregnant population, thus, physicians and patients usually attribute them to the effects of pregnancy. Majority of colorectal cancer diagnosed during pregnancy are rectal carcinomas or in 65 percent of cases.[4] This distribution is opposite of that observed in the general population and thus emphasizes the importance of digital examination for pregnant women. During pregnancy, the increased levels of estrogen and progesterone stimulate the growth of colorectal cancer that have

these receptors.[11,17] This would explain the advanced stages of majority of patients at the time of diagnosis. Minter, et al. (2005) documented the presence of estrogen receptors in about 20 - 54 percent of colon cancer.[11] Furthermore, Geelhoed, et al. reported that 42.8 percent of colon cancer were progesterone receptor-positive.[11] These factors may explain the development of this malignancy in this 40-year old pregnant patient, thus aggravating the disease process.

Dietary factor was also implicated as a risk factor in its development. It is postulated that low dietary fiber content leads to decreased stool bulk, thus increasing fecal transit time in the bowel and an altered bacterial flora of the intestine. In effect, potentially toxic oxidative by-products of carbohydrate degradation by bacteria are present in much higher concentrations in the small stool and are held in contact with the colonic mucosa for longer periods of time. Moreover, the high cholesterol intake in red meat enhances the synthesis of bile acids by the liver, which in turn, may be converted into potential carcinogens by intestinal bacteria.

Pregnancy does not appear to significantly alter the course of the malignant process. Survival of these patients, stage for stage, is similar to that in non-pregnant patients. Conversely, in a report made by Ochshorn, et al. colorectal carcinoma during pregnancy is associated with poor prognosis due to the delay in diagnosis that leads to advanced stages of cancer. Fortunately in this young pregnant patient, the extension of the tumor to the vulva led to early detection.

Colorectal carcinoma can adversely affect pregnancy with only 78 percent resulting in live born infants, mostly because of premature delivery and intrauterine death.[4] Stage for stage, survival is not different from the general population.[4] No pregnant patient with colorectal cancer has been reported in the literature to survive beyond 5 years[11].

Diagnostic evaluation of patients with colorectal cancer includes endoscopy with biopsy, serum CEA and abdominal imaging. Proctosigmoidoscopy done in C.B. revealed an initial intraluminal mass measuring 4 cm x 3 cm, about 3 cm from the anal verge. According to Minter A., 2005, a CEA level obtained prior to surgery provide a baseline to monitor response to treatment and is of prognostic value since increased values prior to surgery are associated with disseminated disease and increased recurrence rates. However, it is not useful for screening due to low sensitivity and specificity since it can be increased during pregnancy. This test was not done to this patient prior to surgery.

Abdominal imaging using ionizing radiation is contraindicated due to radiation teratogenicity particularly in the first trimester. An abdominal ultrasound is an alternative to abdominal CT imaging in pregnant patients. This is useful in evaluating the presence of hepatic metastasis with a sensitivity of 75 percent for detecting macrometastases.[11]

Malignancies discovered during pregnancy usually raise complex therapeutic and ethical dilemmas. Pregnant women confront the diametrically opposed facts of a life-giving and a life-threatening process, a conflict between optimal maternal therapy and fetal well-being. The maternal interest is for an immediate treatment of the tumor. However, the optimal therapy may impose great risks on the fetus. Consequently, either maternal or fetal health or both will be compromised. Thus, both the pregnant patient and her physician are often in a dilemma as to the best course of action.

In this case, two ethical principles are invoked: the Principle of Autonomy and Principle of Beneficence. The first principle safeguards the patient's autonomy, that the pregnant patient must be given freedom to choose alternative courses of therapeutic action based on her values and beliefs.[15] The fetus does not yet possess the capacity to express personal beliefs or perspective on his own interest. Therefore, there is no autonomy-based obligation of the physician to the fetus. C.B. and her husband decided to prioritize the health of the mother and proceed with tumor resection at 24th week age of gestation. Unfortunately, at the time that this decision was made the patient had several medical problems which necessitated correction before the definitive procedure can be carried out.

The Principle of Beneficence, which also includes the Principle of Non-Maleficence, requires the physician to assess objectively the therapeutic options and to implement those that will most

offer the patient the greatest balance of benefit over risks.[15] However, at the same time, the physician has to consider the well-being of the fetus ability to offer the fetus the greatest balance of benefit over risks. In this principle, there is beneficence based-obligation of the physician to the mother and the fetus. Chemotherapy was contemplated in our patient to delay the disease progression with the fetus at 24th week of gestation. Although there is no evidence that exposure to chemotherapy during this period increases the risk of teratogenicity, still there is no prospective studies to support this issue.

The lack of prospective randomized studies has prevented the development of clinical guidelines for most of the issues complicating management for these patients. A general guideline for tumors in association with pregnancy are as follows: if diagnosis occurs in the first half of pregnancy (before 20th week of gestation), the treatment of the cancer should take priority; if it is discovered later, after the 20th week of gestation, the definitive treatment may be postponed until fetal maturity is reached.[5,9,10,11]

C.B. was admitted on her 24th week of gestation and in threatened pre-term labor. Considering the patient's status at the time of admission, a multidisciplinary approach was warranted. She was being co-managed by the Perinatology Service for fetal surveillance and Infectious Disease service due to her hospital acquired infection.

The plan of the service was to terminate pregnancy at 32-34 weeks AOG when a good chance for fetal survival is achieved followed by radical vulvectomy, abdomino-perineal resection and bilateral groin node dissection. During the antepartum period, chemotherapy was contemplated but was not carried out when Pseudomonas infection set in.

Neoadjuvant Chemotherapy

The decision to start antineoplastic therapy in pregnant patients remains a dilemma. With the exception of a recent protocol for breast cancer, guidelines for management of malignancies during pregnancy do not exist.[6] It is universally recognized that a large number of malignant tumors cannot have their treatment delayed until the end of pregnancy due to the high rate of cell proliferation. Thus, fetal well-being may be compromised because a delay in treatment would certainly result in worsening of maternal prognosis. It was contemplated in the case of CB to give platinum-based chemotherapy in the antepartum period to delay disease progression.

Issues that surround the giving of chemotherapy during pregnancy include its teratogenicity and the possible adverse effects on the pregnancy itself. Most cytotoxic agents exert their effects by interfering with some stages of DNA and RNA synthesis, by interrupting essential metabolic pathways and by destroying macromolecules, thus decreasing tumor volume. However, this does not only affect tumor tissue but also normal tissue. During pregnancy, both maternal and fetal tissues may be affected resulting in systemic and teratogenic effects.[6] The teratogenicity of any drug depends on the time of exposure and the dose and characteristics affecting placental transfer. Thus, prior to giving of anti-neoplastic drugs, consideration must be given to the long-term effects of these drugs to the fetus. This should be discussed with the parents.

Case reviews indicate that administration of chemotherapy during the first trimester of pregnancy is associated with higher rates of abortion reported at 20 - 44 percent[6] and fetal malformations reported at 12.7 – 17 percent in contrast to the usual rate of malformation in the general population (1% - 3%).[1] In a study by Doll, et al., the rate of fetal malformation in combination chemotherapy was only slightly higher at 25 percent than that observed with single agents at 17 percent.[1,7]

In contrast, no evidence of an increased risk of teratogenicity in the second and third trimester exists.[7] Non-teratogenic effects of antineoplastic agents include low birth weight, IUGR, spontaneous abortion and premature birth. However, in these reports, difficulties were encountered in separating the effects of the drug from the effect of what is often an advanced malignant process[3,6] and there are no available studies on the long term effects of chemotherapy.

Surgery

Of the primary treatment modalities for cancer during pregnancy, surgery is the type least associated

with adverse fetal sequelae. However, pelvic surgery during the first trimester increases the risk of abortion.[7]

The abdomino-perineal resection (APR) has been considered standard treatment for patients with rectal cancers located within 6 cm from the anal verge. The lesion in C.B. was located anteriorly, 3 cm from the anal verge as demonstrated by proctosigmoidoscopy, hence the procedure was performed. This procedure involves removal of the entire rectum and anus resulting in permanent colostomy. This presents the greatest challenge for the surgeon. A review of the published literature demonstrates that about 80 percent of patients were treated with APR in the 1940's but now, it is performed in only 20-30 percent of patients.[13] The National Institutes of Health (NIH) Consensus Development Conference suggested that a combination of surgical resection, chemotherapy and radiation should be done for patients with resectable tumor and in advanced stage disease. Neoadjuvant chemotherapy and radiotherapy can be done to large tumors to decrease its size prior to surgery.

Vulvectomy, on the other hand, is done in patients with resectable vulvar tumor. Our patient has an enlarging mass at the vulva measuring 4 cm x 5 cm, an extension from the rectal carcinoma, hence, the inclusion of this procedure as part of the definitive management. It involves removal of the vulvar and fatty tissues in all its thickness from the surface to the urogenital diaphragm with a minimum of 1 cm surgical margin.

Disturbances in sexuality is commonly observed in patients with vulvar, vaginal and cervical cancer as compared to ovarian and endometrial cancer. In a study by Andersen, et al., patients who had been treated with vulvar carcinoma were compared with a group of women with respect to sexual function.[20] In this study, the sexual behavior patterns and desires were maintained after therapy. In the case of C.B., it was discussed that sexual function will be compromised as a result of extensive surgery.

Both rectal and vulvar cancers metastasize by direct extension to the adjacent structures and by lymphatic embolization to regional lymph nodes. Lymphatic spread of vulvar lesions involves the superficial lymph nodes from the inguinofemoral area and to the pelvic nodes. The rectum, on the other hand, is divided into three portions, hence, the difference in the lymphatic drainage. The lymph from the middle and upper rectum drains into the inferior mesenteric nodes. Lymph from the lower rectum, below the dentate line drains primarily to the inguinal nodes but can drain into the inferior or superior rectal lymph nodes as well. In our patient, the tumor involves the lower rectum, about 3-6 cm from the anal verge. Lymphatic drainage is likewise via the inguinal nodes. Groin node dissection as was done in our patient consists of removal of all superficial inguinal nodes and femoral nodes medial to the femoral vein.

Fetal Delivery

Delivery should be done by cesarean section because of the risk of dystocia caused by extension of the tumor into the pelvic basin. However, if the lesion is above the pelvic brim, obstruction of labor is not probable hence vaginal delivery can occur.[3] In a report made by Yifat, et al. patients with a rectal mass about 8 cm - 9 cm above the anal orifice successfully underwent vaginal delivery. Although there may be no absolute contraindication to vaginal delivery, the manner of delivery depends on the assessment of the obstetrician. In the case of C.B., the cesarean section was performed because of fetal compromise.

Some authors recommend performing cesarean section in the belief that it would prevent pressure and trauma to the tumor thereby decreasing the risk of bleeding and metastasis[4]. Furthermore, a cesarean section, followed by rectal surgery can be performed simultaneously as what was initially planned in our patient. However, our patient underwent primary cesarean section on her 32nd week of pregnancy and tumor resection was performed four weeks post-partum due to the metabolic problems.

Safe timing for termination depends upon local hospital conditions, considering the capabilities of the neonatal intensive care unit and reports suggested that it can be done between 28 and 32 weeks of gestation. The Philippine Obstetrical and

Gynecological Society (POGS) reports that at 32 weeks AOG there is a 90 percent increase in survival rate.[11] At the Philippine General Hospital (PGH), the survival rate of babies delivered prematurely at 30 weeks AOG and a birth weight of more than 1 kg was reported at 50-60 percent.[12] In our institution, the nursery survival rate among babies delivered at 28 weeks AOG is 20%; 29-30 weeks AOG is 26%; 31-32 weeks AOG is 48% and at 33-34 weeks AOG is 65%. Thus, the outcome of the fetus depends on the capability of the nursery to resuscitate and support the prematurely born child. Prior to her delivery, CB was coordinated with the neonatologist for termination of pregnancy at 32-34 weeks age of gestation.

Upon delivery the baby was noted to be hypoactive, with poor suck and mild retractions for 3 days. The baby's history of exposure to sepsis and clinical condition, necessiteted antibiotic treatment for two weeks. However, he didn't need an incubator and was instead placed in a basinet. He was discharged after four weeks clinically improved with a weight of 1.6 kg.

Final histopathology report of C.B. revealed an adenocarcinoma, well-differentiated, rectum with involvement of the serosa, perineum and rectovaginal septum, Stage IIB (T4NoMx). The postoperative course of C.B. is uneventful except for the perineal wound dehiscence which was promptly managed. At present, the plan is to give chemotherapy using 5-Fluorouracil and radiation therapy.

Summary

A rare case of rectal adenocarcinoma with extension to the vulva in a young pregnant woman was presented. The patient's condition presented a diagnostic and therapeutic challenge. Factors associated with the development of the malignancy in this patient as well as the diagnostic and management dilemma were discussed. She underwent a very extensive surgery for curative intent. A multidisciplinary team approach is vital for optimal delivery of health care to both mother and baby.

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the cervix still 3.5 cm x 3 cm slightly nodular and both parametria smooth. Cervical punch biopsy and endocervical curettage were done and histopath revealed squamous cell carcinoma, large cell non-keratinizing, both specimens consistent with persistent disease. The plan was to give cisplatin 50mg/m^2 and paclitaxel 135 mg/m^2 every 3 weeks for six courses, however she was lost to follow-up. The patient eventually underwent excision biopsy of the infraorbital mass done by the Ophthalmology service, ten months after the initial consult. Histopath revealed basal cell carcinoma, left lower eyelid (Figure 3). Excision was considered complete treatment for this case.

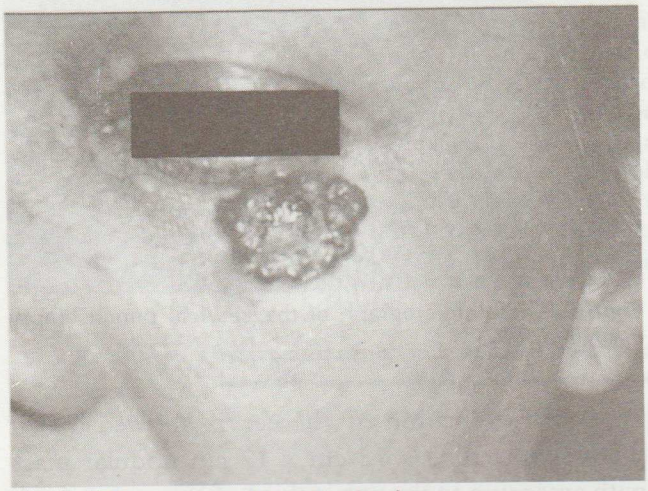

Figure 2. Tumor on the left infraorbital area.

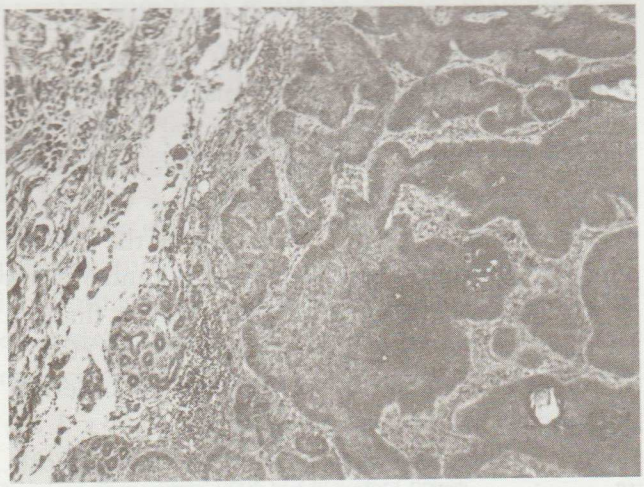

Figure 3. Excision biopsy specimen of the infraorbital mass magnified 40x.

Discussion

Rose evaluated 130 cases of synchronous or metachronous tumors among 5967 patients followed up by the Ohio State University Gynecologic Tumor Registry for the past 44 years from 1939 to 1983. A second malignancy of the lower genital tract occurred in patients with cervical, vulvar and vaginal cancers, 1.6%, 4.3% and 9.6%, respectively supporting the theory of multicentric cancer of the lower genital tract [10]. The phenomenon of multicentricity of epithelial cancer has been demonstrated unequivocally. The clinical implications of this fact were recognized as far back as 1865, when Karl Thiersch speculated that the development of an epithelial carcinoma in the region of a previous excision did not necessarily imply inadequate excision, but in some cases represented continued transformation of an epithelium predisposed to malignant change.[11]

Several questions may be raised by the multiplicity of cancers, for example: Does this imply, a genetic or immunologic aberration or both? An individual developing more than one primary tumor in anatomically and functionally unrelated organs may be considered as cancer-prone. People with a family history of cancer will inherit genetic cancer susceptibility as a risk factor for cancer. Gene mutations influence cancer susceptibility through changes of metabolism and catabolism of carcinogens. Tumor suppressor genes, such as *p53* and *FHIT*, may be candidates for target genes of these risk factors.[12] Genetic instability is also considered as a driving force behind carcinogenesis and the alterations of the length of single repetitive genomic sequences or microsatellite instability, implicating impaired DNA repair mechanism.[13] People with newly diagnosed cancers like our patient and survivors of earlier cancers who have genetic cancer susceptibility, therefore, have an increased risk of multiple primary cancers.

We know that cervical cancer develops from well-defined precursor lesions referred to as either cervical intraepithelial neoplasia or squamous intraepithelial lesions. It is now known that specific types of human papillomaviruses (HPV) are the principal etiologic agents for both cervical cancer

and its precursors The high-oncogenic-risk HPV types associated with invasive cervical cancer produce two oncoproteins, designated E6 and E7, which interact with endogenous cell cycle regulatory proteins, including p53 and retinoblastoma gene. The interaction of virally derived and endogenous cellular proteins converges in deregulation of cell cycle progression and appears to be critical for the development of cervical cancers. However, the development of cervical cancer is a multistep process that cannot be explained simply by infection with specific types of HPV. One additional event that appears to play a role in tumor progression is integration of HPV DNA into the host genome. Integration of HPV DNA frequently disrupts the E2 open reading frames, resulting in overexpression of the E6 and E7 oncoproteins and possibly causing genomic instability. Additional cofactors and mutational events may be important in the pathogenesis of invasive cervical cancers and may include chromosomal rearrangements, loss of constitutional heterozygosity, and proto-oncogene activation.[14]

Basal cell carcinoma of the skin is the most common human cancer, but its molecular-genetic pathogenesis is unclear. Mutation of *p53* (in this case, an overexpression of the *p53* gene) may form an integral part of the pathogenetic sequence and may attempt to explain the pathogenesis of basal cell carcinoma.[15] A recently published article by Zhang, et al. demonstrates that the UV-specific nucleotide changes in 2 tumor suppressor genes, *p53* and *PTCH,* are both implicated in the development of early-onset basal cell carcinoma.[16] Immunologically, the mechanism by which prolonged UV radiation exposure leads to the development of basal cell carcinoma includes suppression of cutaneous immune system and immunologic unresponsiveness to cutaneous tumors. This local effect includes a decrease in Langerhans cells, dendritic epidermal T cells, and Thy1+ cells. Furthermore, systemic proliferation of suppressor T cells and the release of immunosuppressive factors (eg, tumor necrosis factor-a [TNF-a], interleukin 1 [IL-1], prostaglandin [PG], interleukin 10 [IL-10]) are believed to be pathogenic to the development of basal cell carcinoma.[17]

It is quite remarkable if an HPV (human papilloma virus) testing for high risk oncogenic type was done. However, HPV typing is not currently available in the Philippines. Only presence or absence of HPV high oncogenic types via hybrid capture assay using fresh specimen is the one available. HPV testing on paraffin blocks is also not available. Almost all cervical cancers are HPV-positive. However, would testing for HPV for the basal cell carcinoma, explain part of the tumorigenesis or the possibility of metastasis? Recent studies showed that in the frequent detection of HPV. DNA in non-melanoma skin cancer were seen, however, the role of HPV in the development of these cancers remains speculative. Meyer, et al. analyzed different skin tumors, normal skin and hair follicles for HPV DNA using PCR system designed to detect all HPV types known so far. HPV DNA was found in 93% of common warts, 69% of squamous cell carcinoma, 52% of basal cell carcinoma and 41% of actinic keratoses. No individual HPV type predominated. These results indicate that a direct role of HPV in skin carcinogenesis remains questionable.[18] If an attempt was to establish that the carcinoma was a metastasis, considering that metastases are derived from cell clones released from the primary tumor, an HPV testing would have been in order.[19]

The majority of multiple primary neoplasms may occur as a result of chance. Nonetheless different mechanisms have been considered to be involved, such as intense exposure to carcinogens, the effects of chemo-and/or radiotherapy and the influence of genetic predisposition.[20] Epidemiologic investigations on the development of cancer report that as much as 90 percent of all cancers are related to environmental factors such as exposure to chemicals and/or radiation, intake of exogenous hormones, or a history of smoking.[21] Because of the cervix's sensitivity to hormonal influences, it may be considered biologically plausible that oral contraceptives could induce or promote cervical carcinoma. Personal cigarette smoking increases the risk of cervical cancer. The adjusted risk estimate associated with being a current smoker was 3.42; for having smoked for five or more pack-years, it was 2.81; and for having smoked at least 100 lifetime

cigarattes, it was 2.21.[22] Our patient was a known smoker and took oral contraceptive pills.

Is there management peculiar to multiplicity? In this case, the basal cell carcinoma was managed by excision. The cervical carcinoma which was already Stage IIIB was managed by concurrent chemoradiation. Each cancer was treated conventionally as if they occurred separately.

Is prognosis altered by having more than one malignancy? Individually, prognosis for basal cell carcinoma is good with early detection and treatment. Cervical carcinoma stage IIIB has a recurrence rate of 17% following radiation therapy with a 5 year survival rate of 36%.[22] Prognosis in patients with multiple malignacies does not appear to be worse. Management was only altered if prior radiation therapy had been used.[10]

It is therefore imperative that early detection of second primary tumor could alter survival rate. An extensive surveillance and appropriate cytogenetic and molecular studies should be developed to detect multiple primary tumors. Multidisciplinary treatment strategies are important to improve quality of life and survival rates.

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The Burden of Cervical Cancer in the Philippines and Efforts to Combat the Disease*

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Incidence

Worldwide, one woman dies of cervical cancer every 2 minutes, and some 500 thousand new cases of this disease are seen every year. About 80 percent or 400 thousand of these new cases are in developing countries. Of these 400 thousand, 50% or 200 thousand are in Asia. In the Philippines, conservative estimates in 2000 placed the number of cervical cancer cases at between 35 thousand and 70 thousand, to which almost 7 thousand new cases are added every year.

In the Philippines and in many parts of the world, cervical cancer is second only to breast cancer as the most common malignancy that afflicts and kills women. In terms of virulence, however, cervical cancer is a more deadly disease: for every 4 Filipino women who survive cancer of the breast, only 2 or 3 will survive cancer of the cervix.

Costs of the Disease

Cervical cancer is not a disease of old age. The big majority of its victims are women who are at the peak of their biologically and economically productive ages. When a woman dies of this cancer, therefore, a life is not simply lost. Rather, a husband loses a wife, the children lose a mother, and the family is destabilized psychologically, financially and socially. The economy, meanwhile, loses a productive pair of hands.

More than a pair productive hands, however, is lost to the state, which inevitably pays a big part of the cost of treating this disease. Depending on the stage of the disease, the cost of treatment per patient ranges from Php 35,000 to more than Php 703,000. These amounts are prohibitive even to those with income, considering that the national annual average savings per family is only Php 24,000. One way or another, therefore, the government subsidizes a considerable portion of the cost for these families. But for a big part of the population who lives below the poverty level, and who must be treated as charity patients, the government must shoulder all these costs.

This is an irony, because the cost of preventing cervical cancer through early screening could only be as high as Php 800 for a conventional pap smear test in private hospitals, and through an inexpensive acetic acid-based visualization screening method that is being introduced in developing countries worldwide – it could be as low as Php 50 only.

Preventability

Cervical cancer is highly preventable because it has a long pre-cancerous period during which it may be detected and stopped, and every woman can assess her likelihood of being a victim of this cancer.

Pre-cancerous stage. Cervical cancer generally takes as long as 10 years, and may even take 30 years, to develop into a full-blown malignancy. It begins as

* Based on the paper presented by Dr. Cecilia L. Llave at the John Hopkins-JHPIEGO Global Conference on Low-Resource Setting Cervical Cancer Prevention held in Bangkok, Thailand on December 4, 2005.

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an abnormality in cervical cells, and this abnormality is detectable through screening tests that are painless, quick and affordable. At this pre-malignant stage, the disease is highly curable. If every woman who is at risk of developing this disease would subject herself to periodic screening tests, she has a good chance during that big, 10-year window of opportunity to detect and stop this disease before it becomes fatal or more costly to treat.

Risk factors

Every woman may gauge her susceptibility to this disease. This cancer is likely to afflict a woman who:

(1) has warts of the high risk human papilloma virus (HPV) types, in the anal and genital areas
(2) started having sex soon after she began her first menstruation
(3) has or had several sexual partners
(4) has or had a sexually transmitted disease
(5) is a previous or current smoker, or is regularly exposed to secondary smoke
(6) used diethylstilbestrol (DES), a drug for preventing miscarriage of pregnancy, or her mother used it when pregnant with her
(7) has five children or more
(8) belongs in the low socio-economic class
(9) has compromised immune status or poor resistance to diseases

When a woman notes that any of these factors apply to her, she should promptly seek a test for the presence of cervical cancer or its precursor.

Key to Prevention

Early detection and treatment is the key to preventing cervical cancer. Developing countries that applied this concept by means of a sustained national and anti-cervical cancer screening program have greatly benefited. The incidence of cervical cancer in those countries has been reduced by as much as 90 percent, and the number of deaths due to cervical cancer has decreased by 70 percent.

Continuing Menace

Developing countries that lack such sustained national screening programs continue to be menaced by cervical cancer. For the past many decades in the Philippines, for instance, cervical cancer has remained as the second most common cancer among Filipino women.

The recorded incidence of this disease in the country has even increased from an annual average of 4,563 new cases in 1998 to 7,277 new cases in 2005. The specific reason behind this rise is unclear; it may simply be due to improved reporting, or to increasingly unhealthy life-style, or to the rise in carcinogen in an industrializing environment, or to an increase in the sexually transmitted spread of carcinogenic types of HPV warts.

One thing is clear, however: Filipino women are dying of this disease at a rate that has remained unchanged for the past 20 years: of the total new cases of cervical cancer each year, 33 percent or 1 of every 3 die within one year, and 73 percent or nearly 3 of every 4 of the new cases die within 5 years. The reason for this is the late detection of the diseases: in 2 of every 3 new cases diagnosed each year, the malignancy was already at its advanced or fatal stage by the time it was detected.

Population at Risk

Growing at an annual rate of more than 2 percent during the past decades, the Philippine population is estimated at more than 87 million as of 2005. Of this, 28 million are females aged 15 to 64 years old – the age bracket during which cervical cancer develops. The number of women in this group is expected to grow further as the large young segment of the Philippine population matures and is promptly replaced by an even bigger population of infants within a cycle that is largely influenced by a high birth rate and a religious orientation that frowns upon artificial birth control methods.

Among Filipino women aged 15-24 years old, 23 percent or about 1 of every 4 has had sexual contact, exposing them to cervical cancer's risk factors such as early onset of sexual activity, STDs, carcinogenic HPV, and the likelihood of

4. Established the VSMMC as a model referral clinic for cervical cancer cases and other women's reproductive health diseases.

National Policy

Subsequent to the DOH-UP study and the pilot screening project in Cebu, the DOH issued Administrative Order No. 2005-006 which declared the policy of establishing an organized anti-cervical cancer screening program using the AAW test as the primary screening tool in local health units. The AO directed the creation of local registries of women 25-55 years of age, and the coverage of each province by the screening program within the next 7 years. The AO declared other policies and guidelines that likewise reflected the recommendations of the DOH-UP study.

Current Efforts

The most recent effort toward reducing the incidence and mortality rates of cervical cancer in the country began in early 2006. The Johns Hopkins University – affiliated JHPIEGO, and the University of the Philippines-Philippine General Hospital's Cancer Institute (CI), agreed on a project to enhance the country's preparedness and ability to implement a nationwide cervical cancer prevention program. The project subscribes to the use of the AAW test as primary screening tool as advocated by the UP-DOH study and the DOH AO. To this strategy, however, the JHPIEGO-CI initiative adds an innovation: the single visit approach (SUA) in which women who visit a clinic for AAW test will be treated, if tested positive, with cryotherapy during the same visit.

JHPIEGO, which is world renowned for introducing and establishing the basic and adaptable mechanics for the SVA-AAW-cryotherapy approach, will lead in the Philippine project's training, capacity-building and interface aspects. The CI, established in 1938, will contribute its expertise as the country's prime training ground for physician specialists in cancer prevention and treatment, its experience in local cancer research and anti-cancer projects, as well as provide its Cervical Cancer Prevention (CECAP) Center as the project's home and secretariat.

The JHPIEGO-CI project will be implemented in several selected Philippine municipalities which could benefit from a cervical cancer prevention approach that requires little resources. The core capacities established in these areas will be monitored and continuously improved for eventual adoption nationwide.

Conclusion

Cervical cancer has long been a major threat to the health of Filipino women and, by extension, to the health of the Philippine nation. Concerned sectors in the government and in the health community have long been aware that this threat is rooted to the late detection of this disease, and efforts have been addressed to resolve this in the past decades. Initial efforts had failed due to lack of focus, funds, personnel, and other logistical and cultural reasons. New efforts began in the late 1990s and continue today. These efforts view cervical cancer more critically from the perspective of national realities and offer more realistic strategies and solutions. The prospects of success of these new efforts are indicated by several milestones: a team from the Department of Health and the University of the Philippines has studied the problem and recommended realistic solutions; the Department of Health has declared national policies and strategies that reflect these recommendations; a pilot project in Cebu uses approaches that reflect the DOH policy and is showing the feasibility of a locally based and sustained anti-cervical cancer campaign at the provincial level; and a new project with international linkages is expanding the potentials of current local approaches by implementing the innovative single – visit approach to test its adaptability in low-resource Philippine settings.

Cervical Cancer and the HPV Vaccine

Genara A. Manuel-Limson, MD*

Cervical cancer is still a major health problem globally. About half a million new cases are diagnosed yearly, 80 percent of which come from developing countries. The Asia Pacific region contributes 50 percent of the tumor burden from developing countries.

In the Philippines, cervical cancer ranks fifth among the leading cancer sites for both sexes and second among women, next to breast cancer, which is number one. The age standardized rate (ASR) is 22.5 / 100,000. Incidence starts rising steeply at age thirty five. The 2005 Cancer Facts and Estimates estimated 7,277 new cases and 3,807 deaths that year. The reason for this high mortality is the fact that more than 2/3 of our cases of cervical cancer are diagnosed very late.

The human papilloma virus (HPV) has been identified as the necessary cause of cervical cancer. Epidemiologic evidence which attests to this association between HPV and cervical cancer has been strong, consistent, widely reported in several countries and independent of other risk factors (Xavier B, Munoz N). Our own cohort study of the cases of cervical cancer in the Philippine General Hospital confirmed this association. Ninety four percent of our cases of cervical cancer were HPV DNA positive compared to only nine percent among the control.

Although more than 200 papilloma virus types have been described, around 100 types infect humans and, therefore, classified human papilloma virus or HPV (Burd EM, Clifford GM). HPV is a non-enveloped double stranded DNA virus. It is divided into low risk HPV and high risk or oncogenic HPV. The low risk HPV types, the most common being HPV 16 and 11 can cause anogenital warts. The most prevalent oncogenic types are HPV 16 and 18 and together they are found in up to 70 percent of cervical cancer worldwide (Clifford GM, Munoz N). Our own study confirmed these data. Effective measures against just these two most prevalent HPV types should massively reduce mortality from the disease. The key to HPV's effect on cells is two virally encoded proteins, E6 and E7. These proteins interact with the two tumor suppressor genes, p53 and pRb. The p53 activity is often lost in tumors, usually by a combination of mutations and gene deletions. In cervical cancer, the p53 gene is intact and p53 protein is expressed in the transformed cells (Vousden). HPV protein E6 binds with p53 (a tumor suppressor gene) so that when the cells lose this protein (to E6), they can grow uncontrollably. In other words, p53 loses its function as an anti oncogene. Previous studies have indicated that certain co-factors (smoking, early sexual debut, high parity) may be involved in the genesis of cancer of the cervix.

Philippine Prevalence of HPV in Cervical Scrapes

Cases	
356	93.5%
Controls	
381	9.1%

Ngelangel C, Limson G, Munoz N, et al. IARC-WHO-Int. Biological Study Group on Cervical Cancer.

* President, Society of Gynecologic Oncologists of the Philippines, Inc., 1996-1998.

Number and percentage of human papillomavirus (HPV) - positive case and control subjects and odds ratios (ORs) for association between squamous cell carcinoma and adenocarcinoma / adenosquamous carcinoma of the cervix and HPV types.

	Case Subjects							
	Squamous Cell Carcinoma		Adenocarcinoma /Adenosquamous Carcinoma		Control Subjects		OR* (95% confidence interval)	
HPV Type	No.	Percentage of HPV positive	No.	Percentage of HPV positive	No.	Percentage of HPV positive	Squamous Cell Carcinoma	Adenocarcinoma /Adenocarcinoma Carcinoma
Negative	20	6.2	3	9.1	346	90.8	1.0 (referent)	1.0 (referent)
Positive for any HPV type	303	93.8	30	90.9	35	9.2	156 (87-820)	111 (31-392)
Total	323	100.0	33	100.0	381	100.0		
HPV16	130	40.2	8	24.2	5	1.3	506 (178-436)	549 (44-6912)
HPV18	77	23.8	17	51.5	5	1.3	276 (99-771)	948 (97-9240)
HPV45	41	12.7	5	15.2	6	1.6	124 (46-335)	259 (26-2618)
HPV51	10	3.1			0	0.0	cc (19.3-cc)	
HPV52	10	3.1			2	0.5	93 (18-484)	
HPV58	9	2.8			2	0.5	81 (14-480)	
HPV59	5	1.5			0	0.0	cc (19.3-cc)	
HPV66	4	1.2			0	0.0	cc (14-cc)	
HPV X	34	10.5	2	6.1	5	1.3	111 (39-317)	50 (2-456)
Other types	11	3.4	2	6.1	13	3.4	16 (6.1-41.5)	15 (2-116)
Multiple types ~	25	7.7	5	15.2	5	1.3	91 (31-271)	150 (23-973)

* Adjusted for age
~ Included in the calculation of prevalence and ORs for individual types

The Pap smear is known to be the most cost effective cancer screening method yet devised. In developed countries where Pap smear is used widely in organized screening programs, the incidence of invasive cervical cancer has gone down tremendously. In spite of this success, however, no country has really eradicated cervical cancer yet. The development of HPV vaccine which protects against the most prevalent HPV types offers a new tool for the prevention of cervical cancer and its precursor, cervical intraepithelial neoplasia or CIN. Indeed, the HPV vaccine is probably one of the most important health care revolutions in history.

The HPV vaccine is derived from a protein component of the virus – the virus like particle (VLP) produced in yeast or insect cells. The VLP's do not contain the viral genome (no DNA) so that they are non-infectious. They, however, morphologically and anti-genetically resemble or mimic the natural structure of virions so that they can generate potent immune response.

The history of HPV vaccines actually started in 1983 when Zur Hausen established HPV 16, as the leading candidate in the pathogenesis of pre-invasive and invasive cervical neoplasia. In 1991, the first generation HPV virus like particles (VLP) was produced in yeast or insect cells. They do not contain DNA and therefore non-infectious. They structurally and morphologically resemble virions and generate potent immune response. In 2002, Koutsky, et al. reported on the phase II trial of HPV 16 VLP's. This was a double blind, randomized multicenter study consisting of 2,392 women aged 16 to 23 given – 3 doses of placebo or HPV 16 VLP's at Do; Mo2; Mo6. Genital swabs and cervico-vaginal lavage specimens were tested for HPV 16 DNA at enrollment, one month after the 3rd vaccination (Mo12) and every 6 months thereafter. The outcome was persistent HPV infection (2 or more positive

HPV DNA samples). The median follow-up was 7.4 months. Results revealed that the incidence of HPV 16 infection was 3.8 per 100 woman years in the placebo group and 0 per 100 woman years in the vaccine group giving a 100% efficacy, 95% confidence interval (90-100 $p<0.001$). All 9 cases of HPV 16 related CIN occurred in the placebo group.

Diane Harper, et al. also conducted a double blind, randomized controlled trial to assess the safety, immunogenecity of a bivalent L1 VLP vaccines against HPV 16 and 18 incident and persistent infection. This trial involved 1,113 women aged 15-25. Three doses of vaccine formulated with ASO 4 adjuvant given in month 0, 1, 6 or placebo. For 27 months, the subjects were assessed for HPV infection by cytology of self obtained cervico vaginal samples. Results revealed that in the intention to treat to protocol analysis the vaccine efficacy with HPV 16/18 was 91.6% and 100% for incident and persistent infections, respectively. In the intention to treat analysis, the vaccine efficacy with HPV 16/18 was 95.1% against persistent infection and 92.9% against cytological abnormalities.

Results: D. Harper, et al. Trial.

	Vaccine efficacy with HPV 16/18		
	Incident infection	Persistent infection	Cytological abnormalities
1. According to protocol analysis	91.6% (95% C1 64.5 to 98.0)	100% (47.0 - 100)	
2. Intention to treat analysis		95.1% (63.5 - 99.3)	92.9% (70.0-98.3)

The study also found the vaccine to be generally safe, well-tolerated and highly immunogenic which led them to conclude that the vaccine is efficacious in preventing incident and persistent HPV 16 and 18 cervical infection and associated cytological abnormalities and lesions.

A cohort of 776 women were followed up to 53 months. Data revealed that the antibody titers for both HPV 16 and 18 were sustained and high (17 fold higher for HPV 16 and 14 fold higher for HPV 18 compared to antibody titers generated by natural infection).

Another finding is evidence of probable cross-protection against HPV 45 and 31. HPV types which are phylogenetically related to HPV 16 and 18. This cross protection will increase the protection against cervical cancer from 70 percent to 80 percent.

Currently, there is available a quadrivalent vaccine (MSD's Gardasil) which contains HPV 6, 11, 16 and 18. It has been approved for use in several countries like USA, Mexico and Taiwan and recently approved by our own BFAD. This is a prophylactic vaccine to that it is best given before the girl/woman is exposed to the virus – preferably before sexual debut. It may, however, be given even later in the woman's reproductive life. The vaccine is given intramuscularly at month 0, 2, 5. There has been no reported serious adverse effect associated with the vaccine. The problem has been limited to local inflammatory reactions in the injection sites which have been manageable.

Another company is coming up with another HPV vaccine (GSK's candidate vaccine sometime this year. GSK's candidate vaccine is focused on the oncogenic HPV 16 and 18. The adjuvant is ASO_4 3-deacylated monophosporyl lipid A (MPL) plus aluminum hydroxide. This ASO_4 adjuvant system is said to enhance the immune response to VLP's so that higher antibody titers are generated.

Currently, the critical level of antibody titer to protect against cervical cancer and its precursor is not known. It is, however, known that, at least for GSK's bivalent vaccine, the antibody titer remains high as long as 55 months (4.5 years). Just like the hepatitis B vaccine only time will tell whether and when booster doses if at all, are necessary.

With this exciting development, we hope to see the beginning of the end of cervical cancer.

Updates on Antibiotic Therapy for Septic and High Risk Patients*

Ricardo M. Manalastas Jr., MD**

The is divided into two parts: first is the 2002 Infectious Disease Society of America (IDSA) Guidelines for Febrile Neutropenia, and second is the discussion on the Extended-Spectrum Beta-Lactamase (ESBL) producing organisms.

More and more, the gynecologist who provides health care to women with gynecologic cancer is confronted with the problems associated with the adverse side effects of the treatment administered. Infection is one such common, and unfortunately, highly serious problem. Extensive surgery, radiation and most especially systemic chemotherapy lead to the suppression of the immune system in various ways. One of the most significant deficiencies that develop is neutropenia, defined as an absolute neutrophil count of less than 500/mm^3. It is on this background that the development of fever, defined as a temperature of 38.3°C or higher, signals the onset of a potentially serious, life threatening infectious complication in the woman with gynecologic cancer.

The algorithm for the initial management of febrile neutropenia formulated by the IDSA in 2002 is shown in Figure 1.

The initial step requires the classification of the patient into whether she is low- or high-risk. Certain factors have been identified that favor a low-risk for serious infection in a febrile patient with neutropenia. These factors are listed in Table 1.

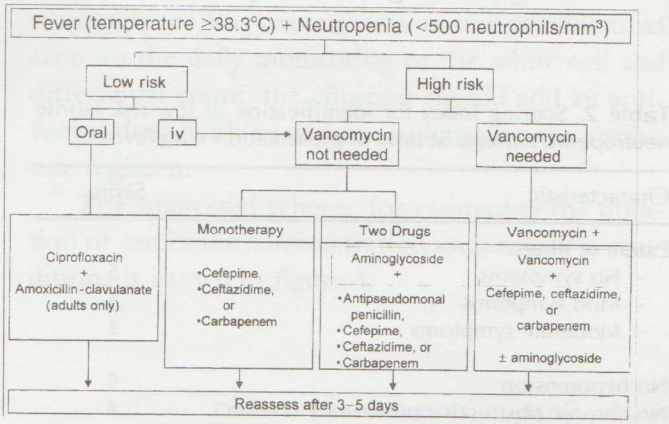

Figure 1. Algorithm for the initial management of febrile neutropenic patients.

Table 1. Factors that favor a low risk for severe infection among patients with neutropenia.

· Absolute neutrophil count of 100 cells/mm^3
· Absolute monocyte count of 100 cells/mm^3
· Normal findings on a chest radiograph
· Nearly normal results of hepatic and renal function tests
· Duration of neutropenia of <7 days
· Resolution of neutropenia expected in <10 days
· No intravenous catheter-site infection
· Early evidence of bone marrow recovery
· Malignancy in remission
· Peak temperature of <39.0°C
· No neurological or mental changes
· No appearance of illness
· No abdominal pain
· No co-morbidity complications[a]

[a]Concomitant condition of significance (e.g., shock, hypoxia, pneumonia or other deep-organ infection, vomiting or diarrhea).

* Lecture presented during the Joint SGOP-Infectious Disease Specialists in Obstetrics & Gynecology Midyear Convention, March 11, 2007.

** Chief, Section of Infectious Disease, Department of Obstetrics & Gynecology, Philippine General Hospital, University of the Philippines Manila.

clinician could stop the antibiotics when afebrile for 5-7 days in the patient who was assessed as low risk initially and is clinically well on reassessment. However, the clinician should continue antibiotics in the patient who was assessed as high risk initially, or has an absolute neutrophil count of less than 100 cells/cumm, or has mucositis, or has unstable clinical signs on reassessment.

If the patient has persistent fever, and the absolute neutrophil count is more than 500 cells/cumm, the clinician could stop the antibiotics 4-5 days after the absolute neutrophil count increases to more than 500 cells/cumm, then reassess.

If the patient who has persistent fever and the absolute neutrophil count is still less than 500 cells/cumm, the clinician should continue antibiotics for 2 weeks, then reassess. Antibiotics can be stopped if the patient shows no sign of disease and her condition is stable.

Antiviral drugs are not recommended for routine use unless clinical or laboratory evidence of viral infection is evident

Granulocyte transfusions are not recommended for routine use as well.

The use of colony-stimulating factors is not routine but should be considered in certain cases with predicted worsening of the clinical course.

The use of antibiotic prophylaxis for afebrile neutropenic patients is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent Pneumocystis carinii pneumonitis. Antifungal prophylaxis with fluconazole and antiviral prophylaxis with acyclovir and ganciclovir are warranted for patients undergoing allogenic hematopoietic stem cell transplantation.

The second and last part of the presentation is a discussion of the extended-spectrum beta-lactamase producing (ESBL) organisms and their potential impact on infections in high risk patients including the neutropenic hosts under discussion.

Pathogenic organisms have recently been observed to manifest resistance to the third-generation cephalosporins, azthreonam and the fluoroquinolones. The main reason for this is their ability to produce the so-called ESBL or the extended-spectrum beta-lactamase enzymes. These plasmid-mediated bacterial enzymes with a broader spectrum of activity are able to hydrolyze a wide variety of penicillins and cephalosporins. ESBL evolved by a genetic mutation from native beta-lactamases, and is believed to be the effect of selective use and overuse of the newer beta-lactams. A prominent characteristic of organisms with ESBL is their resistance to multiple new generation antibiotics including third-generation cephalosporins and quinolones.

The susceptibility of the gram negative bacilli (Enterobacteriaceae) in the Philippines as recently reported (Hsueh PR, 2006) are shown in figures 5 and 6.

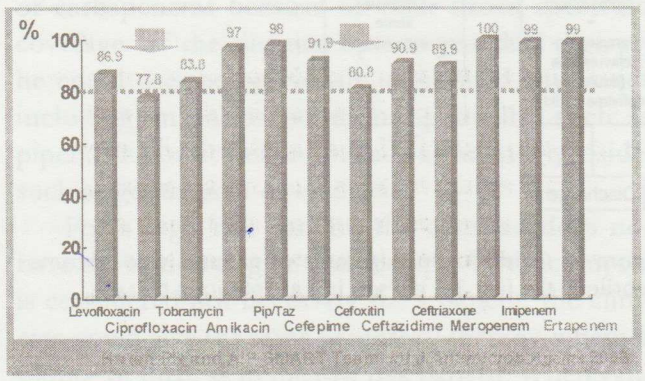

Figure 5. Susceptibility of enterobacteriaceae. Smart, 2004, IAI, Philippines (N = 99).

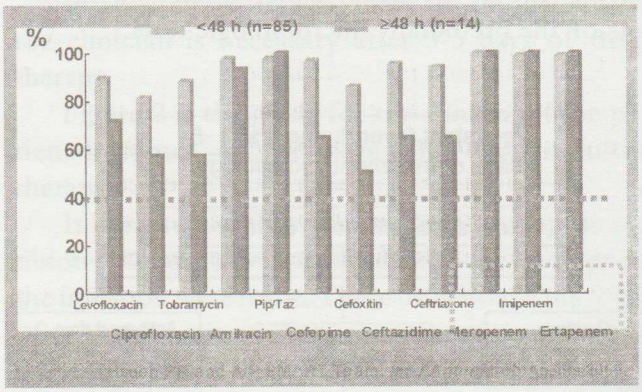

Figure 6. Susceptibility of enterobacteriaceae. Smart, 2004, IAI, Philippines

The findings from this report show that the overall susceptibility to the cephalosporins and quinolones tested was low for nosocomial isolates. Susceptibility to amikacin was high. Carbapenems

remain reliably active against the Enterobacteriaceae, including strains resistant to other antimicrobials, and those with ESBLs.

The carbapenems, e.g., Imipenem, meropenem and ertapenem, and their relative activity against various organisms including ESBLs are shown in table 3.

Table 3. Carbapenems.

	Enterics (ESBL)	Anaerobes	Ps. aeroginosa/ A.baumannii
Imipenem	+++	+++	++/+++
Meropenem	+++	+++	+++/++
Ertapenem	+++	++	±/±

As shown, Imipenem and meropenem show almost similar activity against most organisms. Ertapenem however, show limited activity against Pseudomonas and Acinetobacter.

Table 4 shows the recommended treatment for infections with ESBL-producing organisms.

Table 4. Recommended treatment for infections with ESBL-producing organisms.

Infection type	First line	Second line
Urinary tract infection	Quinolone*	Amoxicillin/ clavulanate
Bacteremia	Carbapenem	Quinolone*
Hospital-acquired pneumonia	Carbapenem	Quinolone*
Intra-abdominal infection	Carbapenem	Quinolone* (plus metronidazole)
Meningitis	Meropenem	Intrathecal polymyxin B

Paterson DL and Bonomo RA. Clin Microbiol Rev 2005;18: 657-686.

As shown, the carbapenems are first line antibiotics in patients with bacteremia, hospital-acquired pneumonia and intra-abdominal infections suspected or confirmed to have ESBL-producing pathogens.

Summary

The presentation included the 2002 IDSA guidelines for the use of antimicrobial agents in neutropenic patients with cancer. This was followed by a discussion of the role of ESBL-producing bacterial pathogens including the role of carbapenems in infections involving these patients.

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