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INSIDE

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Clinical Oncology Alert's Editor, William Ershler, MD, is on the speaker's bureau for Wyeth and does research for Ortho Biotech.

Weekly Neoadjuvant Paclitaxel for Breast Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC

Synopsis: *Paclitaxel, administered weekly, compared to once-every-3-weeks in a trial of primary systemic (neoadjuvant) treatment for operable breast cancer was shown by Green and colleagues at M.D. Anderson and Brown University to provide comparable clinical responses but superior rates of pathological complete response (pCR) and breast conservation. Both the weekly and q3 week regimens were followed by 4 cycles of fluorouracil/doxorubicin/cyclophosphamide (FAC).*

Source: Green MC, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol.* 2005;23:5983-5992.

THE CURRENT STUDY WAS DESIGNED TO COMPARE THE ANTI-TUMOR efficacy of weekly vs once-every-3-week dosing of paclitaxel in the primary systemic treatment (PST) of patients with invasive breast cancer before surgery. For this, patients seen at either the University of Texas M.D. Anderson Cancer Center (Houston, TX), or at the Brown University Oncology Group (Providence, RI) with stage I-IIIA breast cancer were randomly assigned to receive neoadjuvant paclitaxel in doses administered either weekly (for a total of 12 doses of paclitaxel) or once every 3 weeks (4 cycles), followed by 4 cycles of fluorouracil/doxorubicin/cyclophosphamide (FAC) in standard doses administered every 3 weeks. Two different doses of paclitaxel were used based upon lymph node status defined by ultrasound and fine needle aspiration. Outcome measures included clinical response and extent of disease in the breast and lymph nodes after completion of all chemotherapy.

A total of 258 patients were enrolled at the 2 participating centers. Of these, 110 patients had histological evidence of lymph node involvement and 148 did not. Weekly paclitaxel

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followed by FAC was administered to 127 patients and once-every-3-weeks paclitaxel followed by FAC was administered to 131 patients. Clinical response to treatment was similar between groups. Patients receiving weekly paclitaxel had a higher pathologic complete remission (pCR) rate (28.2%) than patients treated with once-every-3-weeks paclitaxel (15.7%; $P = 0.02$) and the weekly treatment group also had a higher breast conservation rate ($P = 0.05$).

COMMENTARY

The use of weekly chemotherapy, notably with taxanes has become a fairly popular approach, primarily for patients with metastatic breast cancer. Its popularity, although balanced by the necessity for increased office visits, is based upon demonstrated equivalent efficacy achieved with less toxicity.[1] The current research, reported initially at ASCO in 2001, is finally in manuscript form and any delays in publication may be attributable to the analysis required for a fairly complex clinical trial design. For those women who were found to be node positive (by ultrasound and fine needle aspirate) and randomized to weekly therapy, a more intensive than usual dosing schedule was initially employed. The initial cohort (n = 13) received 175 mg/m^2 by 3 hour infusion every week for 6 weeks followed by a 2-week break. This schedule resulted in a high percentage of grade 3 neurotoxicity (76.9%). The next cohort (n = 14) received paclitaxel at 150 mg/m^2 by the same schedule. In this group, 50% developed grade 3 neurotoxicity, but neutropenia occurred commonly, necessitating treatment delays. Accordingly, all subsequent node positive subjects (n = 29) were treated with the same relatively high dose for weekly therapy (150 mg/m^2) over a period of 3 hours for 3 weeks straight, followed by a 1-week break. This three week course comprised one cycle, and 4 cycles were completed before switching to FAC. Node negative patients randomized to weekly paclitaxel received 80 mg/m^2 administered over 1 hour every week for 12 weeks. All patients (node positive and node negative) randomized to the once-every-3-week dosing received paclitaxel 225 mg/m^2 administered as a continuous infusion over a period of 24 hours on day 1 of each of 4 cycles. All patients (weekly or once-every-3-week paclitaxel), upon completion of the paclitaxel course, were treated with standard doses FAC.

This report is likely to be just one of several that might come from this trial. Short-term outcomes (clinical response, which was equivalent, and pathologic CR rate, which favored the weekly paclitaxel schedule) are used as surrogates of the more meaningful data (disease free and overall survival) for which it is likely data will be available soon. Nonetheless, it is likely that pCR will correlate with longer disease free and overall survival, as has been demonstrated previously.[2]

Thus, although the study design presents logistical problems for rigorous analysis, it is likely that weekly neoadjuvant paclitaxel will prove superior to the once-every-3-week schedule when the final reports are in and the findings are confirmed by other trials. It should be noted, however, that the dose and schedules chosen, particularly the 24 hour infusion of paclitaxel employed in the once-every-three-week schedule, but also in FAC, may be a bit outdated, having given way to the shorter infusion times for q3-week paclitaxel (3 hours) and the more conveniently administered doxorubicin/cyclophosphamide regimens. ■

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EDITORIAL GROUP HEAD: Lee Landenberger.
MARKETING PRODUCT MANAGER: Gerard Gernazian.
MANAGING EDITOR: Robert Kimball.
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Prognostic Indexes in Follicular Lymphoma: A Comparison of Different Prognostic Systems

ABSTRACT & COMMENTARY

By Stuart M. Lichtman, MD, FACP

Associate Attending, Memorial Sloan-Kettering Cancer Center, Commack, NY

Dr. Lichtman reports no financial relationship to this field of study.

Synopsis: *In this series, all 3 indexes, IPI, ILI, and FLIPI, were useful to classify FL patients into differentiated risk groups, although the FLIPI identified a larger proportion of high-risk patients than the IPI and ILI.*

Source: Perea G, et al. Prognostic indexes in follicular lymphoma: a comparison of different prognostic systems. *Ann Oncol*. 2005;16:1508-1513.

Follicular lymphoma (FL) is most commonly seen in middle-aged patients and accounts for ~30% of newly diagnosed non-Hodgkin lymphomas (NHL). Despite the prolonged median survival time, ~10 years, progression-free survival (PFS) and overall survival (OS) are poor in some patients. Several attempts to build up a prognostic index that is useful to make risk-adapted treatment recommendations have been made. The International Prognostic Index (IPI) has been successfully applied to patients with FL, but it seems to have a limited discriminating power as most patients are in the favorable- or the intermediate-risk groups.[1] In the last few years 2 specific prognostic scores have been proposed: the Italian Lymphoma Intergroup Index (ILI)[2] and, more recently, by an international group, the Follicular Lymphoma International Prognostic Index (FLIPI).[3] The IPI and ILI indexes have been applied in FL patients with different success. The aim of this study was to apply the 3 prognostic indexes in a large group of patients with FL and to try to determine the relative merits of each of them.

Four hundred and sixty-five patients with a histologically confirmed diagnosis of FL grade I or II according to the WHO classification, consecutively diagnosed at 5 hospitals from Barcelona between January 1976 and December 2001, were initially considered for this study. Data needed to calculate all 3 indexes were finally obtained from 411 patients. The median follow-up of surviving patients was 73 months (range, 6-292). Patients received varying first-line treatments: 18 patients (4%) did not receive any treatment, since a watch-and-wait policy was adopted; 36 patients (10%) were treated with radiotherapy and/or surgery alone; 58 patients (14%) with a single alkylating agent (cyclophosphamide or chlorambucil); 51 patients (12%) with a combination chemotherapy regimen without an anthracycline (basically cyclophosphamide, vincristine and prednisone); 21 patients (5%) were treated with fludarabine combinations; and 227 patients (55%) with a chemotherapy regimen with an anthracycline (CHOP/CNOP). Response to treatment was assessed within 3 months after therapy was completed. In general patients were evaluated every 3 months during the first year, every 4 months during the second year, every 6 months during the next 3 years, and every year thereafter. Response after treatment was available in most patients: 190 (49%) achieved a complete response (CR) with initial therapy and 149 (39%) a partial response (PR), whereas 45 patients (12%) failed to respond to treatment.

The IPI was calculated according to the International Non-Hodgkin's Lymphoma Prognostic Factors Project. The variables used were age (< 60 vs > 60 years), performance status (Eastern Cooperative Oncology Group performance status 0 or 1 vs > 2), Ann Arbor stage (I-II vs III-IV), extranodal involvement (< 2 vs 2 or more sites) and serum lactate dehydrogenase (LDH) level (normal vs high). Three risk groups were defined by IPI: score 0-1, low-risk; score 2, intermediate-risk; score > 3, high-risk. The high-intermediate and high-risk groups were joined to form a single high-risk group for comparisons with the other indexes.

The ILI index was calculated as detailed by the Italian Lymphoma Intergroup. Six variables were used to construct this index, 3 of them were also included in IPI (age, extranodal involvement and LDH level). The other 3 variables considered were presence of B-symptoms, male sex and erythrocyte sedimentation rate > 30 mm/h. Depending on the number of adverse prognostic factors (0-1, 2, or > 3), patients were classified into low-, intermediate- or high-risk groups.

The FLIPI was calculated according to the Follicular Lymphoma International Prognostic Project. The variables used to classify patients according to the FLIPI index were age > 60, advanced stage (III-IV), increased serum LDH, hemoglobin level < 12 g/dL and nodal involvement 5 or more sites). Three risk groups were considered: score 0-1, low risk; score 2, intermediate risk; and score > 3, high risk.

COMMENTARY

This report compares 3 prognostic indexes for FL (ie,

the IPI, ILI and FLIPI) in an attempt to determine the merits of each one of these prognostic models. The IPI, initially designed for use in aggressive lymphomas, is easily applicable in clinical practice, and is also valuable in low-grade lymphomas. A major setback with the IPI is that only a small percentage (~8-11%) of patients with FL are included in the high-risk group. The ILI and FLIPI indexes, specifically designed for FL, also include variables that are easy to calculate, and separate patients into different risk groups. Regarding the FLIPI, patients from the current series were distributed in 3 different survival groups, with an OS probability at 5 and 10 years very similar to those previously reported, although in this series a higher proportion of patients were included in the high-risk group (38% vs 27%). The FLIPI seems to classify a larger number of patients into the high-risk group than IPI and ILI, even when only younger patients (> 60 years old) are considered: 14%, 16% and 20% of patients were included in the high-risk group after applying IPI, ILI and FLIPI indexes, respectively. According to these results, all 3 systems are useful to distribute FL patients into different risk groups, although the ILI index was especially valuable to separate high-risk patients, because in contrast with the other 2 indexes, differences in survival between low-risk and intermediate-risk patients were less significant. Of note, median survival of patients in the high-risk group is quite long (30-34 months) whatever the prognostic system employed. Because of this, Perea and colleagues argue that prognostic indexes for FL, as currently devised, are not useful for making treatment decisions.

The prognostic assessment of patients with FL could be improved by using other variables. In addition, the prognostic impact of genomic aberrations in patients with FL has also been investigated and a negative impact has been described for deletions of 6q. The whole-genome microarray analysis of gene expression has also been applied in FL and a survival predictor model constructed according to the gene expression signatures derived from non-malignant immune cells presents in the tumor at diagnosis.[4] These biological findings may contribute significantly to risk assessment in patients with FL.

In conclusion, all 3 prognostic systems investigated (IPI, ILI, and FLIPI) were useful to identify patients with FL and different survival probabilities. In this series, however, the FLIPI identified a larger number of patients in the high-risk category. Future research should aim at improving the prognostic assessment of patients with FL by combining clinical variables with recently discovered biological variables. ■

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DIC and Hemolysis after WinRho Treatment for ITP

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Section of Hematology/Oncology, University of Chicago

Dr. Artz reports no financial relationships with this field of study

Synopsis: *Summarizing adverse events reported to the FDA, 6 definite cases of intravascular hemolysis (hemoglobinuria/hemoglobinemia and/or DIC) are detailed after administration of anti-D IGIV (WinRho). Several patients developed intravascular hemolysis after previously uncomplicated anti-D IGIV. Five patients were adults and all died. This study not only demonstrates that potentially fatal acute intravascular hemolysis may occur after anti-D IGIV and the importance of post-marketing surveillance.*

Source: Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0)(D) immune globulin intravenous administration for immune thrombocytopenic purpura. *Blood*. 2005. 106:1532-1537.

The wide clinical spectrum of idiopathic or immune thrombocytopenic purpura (ITP) presents a challenge in determining the need and type of treatment. Although steroids are most commonly used, IVIG and Rho(D) immune globulin intravenous (anti-D IGIV, WinRho SDF), are often used solely, or in combination, with steroids. The mechanism of anti-D IGIV involves clearance by splenic macrophages of sensitized D antigen positive erythrocytes.[1] Although the mechanism of action presumably leads to some degree of extravascular hemolysis, in the initial clinical trials, 2 cases of hemo-

globinemia or hemoglobinuria were noted and subsequent review summarized 15 cases, suggesting the possibility of intravascular hemolysis as well.

Gaines summarizes the adverse events leading to intravascular hemolysis evidenced by hemoglobinemia, hemoglobinuria or disseminated intravascular coagulation reported to the Food and Drug Administration (FDA) of anti-D IGIV after licensure in 1995. Six cases meeting the defined case definition were received between 1999 and 2004. Five additional cases were received, but inadequate data led to exclusion. Among the 6 patients, all 5 adults died within 3 to 10 days of receiving therapy. The only child in the series survived. The mean decrease in hemoglobin from baseline was 5.8 g/dL, not accounting for possible red cell transfusions. Several patients previously received anti-D IGIV safely before developing severe intravascular hemolysis, indicating prior treatment does not ensure safe retreatment.

COMMENTARY

ITP is frequently treated by hematologists and oncologists. In light of the chronic relapsing nature of ITP, complications of therapy may hold equal weight to efficacy in treatment decisions.

Two important implications arise from this study. First, treatment with anti-D IGIV may lead to intravascular hemolysis and death. Clearly, adverse events reported to the FDA under represent the actual frequency but also may be biased in reporting only the most severe cases. Another problem may be that cases of ITP could actually represent occult TTP/HUS or DIC, which are at least predisposed to this complication. Nevertheless, this study and the prior work confirm this potential complication of anti-D IGIV. More problematic, several patients developed intravascular hemolysis after prior treatment, which suggests close monitoring, may be needed after each treatment. Since the hemolysis was very acute, it would be reasonable to consider reevaluating the patient the same day or the following day of therapy. Despite the uncommon but serious problems with anti-D IGIV, the attendant complications of corticosteroids and IGIV suggest they do necessarily represent safer alternatives.

A second important implication involves reporting adverse events to the FDA. Increasingly, post-marketing reports, typically from community practicing physicians, alert physicians to unexpected but serious complications. We should all have familiarity with using the MedWatch system from the FDA (www.fda.gov/medwatch).

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Second-Line Irinotecan and Carboplatin for Advanced Ovarian Cancer: Phase 1

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a phase I trial for patients with advanced ovarian cancer, irinotecan and carboplatin were administered at 6 different dose levels to determine maximum tolerated dose. The dose-limiting toxicity was hematologic (neutropenia and thrombocytopenia). The recommended dose for the Phase II study was irinotecan 60 mg/m² on Days 1, 8, and 15 and carboplatin 5 mg/mL (AUC) on day 1, repeated every 4 weeks. Of note, of the ten patients with measurable disease, criteria for treatment response were achieved in 5. This level of response bodes well for this combination.*

Source: Yonemori K, et al. A phase I study and pharmacologic evaluation of irinotecan and carboplatin for patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy. *Cancer*. 2005;104: 1204-1212.

Ovarian cancer is the leading cause of death from malignancy in women. Although 60 to 80 percent of women with advanced ovarian cancer treated with platinum-containing chemotherapy initially respond, the responses for many are only temporary. Thus, a focus of clinical research remains the definition of optimal treatment for relapsed patients.

The purpose of the current study was to establish the maximum tolerated dose (MTD) for irinotecan and carboplatin when used in combination for patients with advanced ovarian cancer who had received prior platinum-based therapy. Additionally, pharmacokinetic and pharmacodynamic studies were performed.

Irinotecan (CPT-II), a DNA topoisomerase I inhibitor, has proven useful in the setting of drug resistance, and preliminary evidence has suggested potential synergism with carboplatin. Ovarian cancer patients with active disease who had prior platinum-containing chemotherapy, whether platinum-sensitive or platinum-resistant, were enrolled (n = 19) between August 1996 through July 1999. Carboplatin was administered as a 60 minute intravenous infusion on Day 1 and was followed by irinotecan, which was administered as a 90-minute infusion on Days 1, 8, and 15. Six different dose levels of the

2 drugs were explored.

The dose limiting toxicities were hematologic (Grade 4 neutropenia and/or thrombocytopenia). The response to therapy was assessed using World Health Organization (WHO) criteria and 5 of the 10 patients with measurable disease were found to have an objective response.

Based on these results, irinotecan and carboplatin appear to be a reasonable option for women with advanced ovarian cancer who have already received platinum based chemotherapy. The recommended dose for Phase II investigation is irinotecan 60 mg/m^2 on Days 1, 8, and 15 with carboplatin given on day 1. The dose of Carboplatin based on the Chatelut formula, was 5 mg/mL (AUC) on Day 1 repeated every 4 weeks.

COMMENTARY

By design, this was a Phase 1 trial with a goal of determining MTD was achieved by standard clinical trial methodology. It is noteworthy that half of the patients with measurable disease met established criteria for response. Thus, the rationale for a Phase II trial with this combination is strengthened, both for those who have demonstrated platinum resistance and for those who have not.

Low-Income Women, Breast and Gynecologic Cancer, and Depression and Anxiety

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Source: Ell K, et al. Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer. *J Clin Oncol*. 2005;23: 3052-3060.

THE PREVALENCE OF DEPRESSION AMONG LOW-INCOME, ETHNIC minority women with breast or gynecologic cancer is largely unknown, but limited formal screening programs and restricted access to effective therapies would suggest the number to be high. The trial by Ell and colleagues represents a unique insight into the scope of the problem. The principal aims in this report were to quantify the prevalence of depression, to evaluate the receipt of antidepressant medications or counseling services, and to examine the correlates of depression. To do this, they identified 500 women with gynecologic or breast cancer who were currently participating in an ongoing randomized trial of structured case management intervention in order to improve adherence to cancer treatment. From this group, 472 women were receiving cancer care in an urban public medical center and were surveyed for depression, anxiety and pain according to structured questionnaire models. The queries were conducted before and during cancer therapy or during active follow-up.

They found that 24% of this population reported moderate-to-severe levels of a depressive disorder. Depression was more commonly reported in breast cancer patients (30%) than in gynecologic cancer patients (17%). Only 12% of women were receiving medications for depression despite meeting criteria for major depressive disorder (MDD). As anticipated, women receiving medication were less likely to have major depression and pain symptoms. Only 5% reported seeing a counselor or participating in a cancer support group. Surprisingly, neither cancer stage nor treatment status were correlated with depression.

Correlates of MDD were: breast cancer (vs gynecologic cancer), younger age, greater functional impairment, poorer social and family well-being, anxiety, co-morbid arthritis, and fears about treatment side effects. Ell et al concluded that MDD is prevalent among ethnic minority, low-income women with breast or gynecologic cancer. It appears to be correlated with pain, anxiety, and health-related quality of life. Because these women are unlikely to receive depression treatment or supportive counseling, there is a need for routine screening, evaluation, and treatment in this population.

COMMENTARY

Studies evaluating the effect of cancer, cancer treatment and cancer education on emotional well-being are mounting and bring a consistent message—depression, anxiety, and pain are under-appreciated, under-diagnosed, under-treated and disparately addressed among ethnic minority and impoverished socioeconomic women. Burdensome enough through this oversight, poor access to care even when these maladies are appropriately identified only troubles these women more and represents a daunting challenge for our

under-resourced public health system. Nonetheless, the article by Ell et al demonstrates that basic screening is an important first step.

The study is a nested cross-sectional survey of women included in an ongoing randomized trial assessing the impact of structured case management for cancer patients. The intent of this trial is to determine not only the barriers to care but to assess a program to improve adherence to cancer treatment and follow-up. This is an important feature to consider because the results identified in this nested trial represent a point in time of a cohort undergoing care for malignancy—a fluid variable, changing over time. Despite the stasis of the observation, there are several impressive figures identified. First, nearly 1 in 4 of their mostly indigent, minority population met the validated criteria for MDD. While the diagnosis was more commonly identified in breast cancer patients, neither group received adequate therapy for it; and even fewer were in supplementary support groups or counseling. Fully 20% of the women with MDD reported suicide ideation. Other correlates to the diagnosis included younger age, pain, anxiety, and arthritis. Second, barriers to health care were common in depressed women and included many factors which could be positively influenced with directed case management such as understanding treatment recommendations, fears of receiving treatment, inability to get medication, concerns of lost wages, and reminders of appointments. Third, fewer than 1 in 8 women with MDD were receiving active treatment.

Data in this study certainly support Ell et al's contention that health care practitioners need to investigate ways to improve depression care in these patients. We look forward to the subsequent information obtained from the longitudinal and interventional study Ell et al are currently conducting. As limitations and barriers to care and case management are relieved, better outcomes to cancer therapy and hopefully survival will be realized. ■

Additional Reading

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Are Fertility-Sparing Procedures Safe for Women with Ovarian Borderline Tumors? Probably.

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *Fertility-sparing surgery for ovarian LMP tumors is an option for motivated patients. Preservation of the contralateral adnexa increases the risk of recurrence, but surgical resection is usually curative.*

Source: Rao GG, et al. Fertility-sparing surgery for ovarian low malignant potential tumors. *Gynecol Oncol*. 2005;98: 263-266.

It has been well documented that women diagnosed with low malignant potential (LMP) tumors have an excellent prognosis with few recurrences identified in those undergoing definitive resection. However, many of these cases occur in women of childbearing age in whom fertility may be desired. Limited evidence to date has suggested that subtotal resection is not associated with worsening prognosis although recurrence risk is increased. In evaluation of this objective, Rao and colleagues examined the outcomes of 38 patients with LMP tumors who underwent fertility-sparing operations as primary management of their disease. Most had unilateral oophorectomy; 5 underwent cystectomy only. Although formal staging wasn't obtained in all cases, only 4 were not apparent stage I. No patients received adjuvant therapy. At a median 26 months of follow-up 6 patients had recurred (16%); 5 in a remaining ovary, in which all were cured following subsequent resection. Five women delivered 6-term infants during post-treatment surveillance. Rao and colleagues conclude that given these characteristics, well-informed patients might safely choose surgical therapy which preserves their fertility. Although recurrence may be experienced, surgical resection is generally curable

■ COMMENTARY

Most women diagnosed with an ovarian malignancy

have invasive, advanced-staged disease requiring aggressive cytoreduction and adjuvant chemotherapy. The track record in successful management for these patients is well described and while improving, is, in general, poor. On the other end of this spectrum, tumors of low malignant potential are characterized by limited extra-ovarian disease at presentation, long periods of disease-free survival and infrequent need for systemic adjuvant therapies. While some of these tumors can be fatal, particularly in those patients in whom inoperable disease attains a progressive or an invasive phenotype, the majority follows a more benign course compared to their invasive counterpart. Surgical staging studies of women with these neoplasms have documented that thorough abdominal and pelvic sampling will upstage approximately 20% of apparent stage I cases.[1-4] However, it has been increasingly documented that re-operating to formally stage a patient with a *surprise* LMP final pathological diagnosis is of little value. Nonetheless, receiving the diagnosis of LMP intraoperatively generally promulgates formal surgical staging as subsequent upgrading to invasive disease can occur in 5-30%. In patients with unstaged invasive lesions the stakes are higher; and the management considerations in this situation are to re-operate for formal staging or empiric multi-agent chemotherapy. With these caveats, a young woman undergoing surgical exploration for adnexal pathology should have a discussion that not only incorporates the possibility of cancer but also the procedures to be undertaken in this situation. For the motivated patient who understands the attendant risks of subtotal resection in the event of LMP, fertility-sparing procedures are an option. Data from the current series as well as others would support this management pathway.[5] Staging biopsies are still obtained but resection of all fertility organs may be omitted. The decision to remove these retained organs after childbearing is less definitive but generally recommended if it is an organ responsible for persistent or recurrent disease.

Advanced reproductive techniques are redefining what "fertility-sparing" entails. A retained uterus without ovaries permits surrogacy, as well as subcutaneously implanted ovarian tissue in the absence of ovaries or a uterus. Such extremes are infrequently encountered but underscore pre-operative counseling necessary for women with adnexal masses in whom, prospective education can maximize options for fertility-desiring women. ■

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CME Questions

11. Paclitaxel, when administered weekly, as opposed to once-every-3-weeks in the neoadjuvant (primary systemic therapy) for breast cancer was shown by Green and colleagues to have more optimal:
a. clinical response rates.
b. pathologic complete remission (pCR) rates.
c. disease free survival.
d. overall survival.
e. All of the above

12. The dose-limiting toxicity revealed in the Phase I investigation of irinotecan and carboplatin for ovarian cancer patients was:
a. gastrointestinal (diarrhea).
b. hematologic (neutropenia, thrombocytopenia).
c. neuropathy.
d. skin rash.

13. What serious complication has been reported after use of anti-D IGIV for Immune thrombocytopenic purpura (ITP)?
a. Pulmonary embolus
b. DIC and hemoglobinuria
c. Cancer
d. Stroke

Answers: 11 (b); 12 (b); 13 (b)

CME Objectives

The objectives of *Clinical Oncology Alert* are:
- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

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More on Breast Cancer

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

The Use of Prophylactic Antibiotics for Neutropenia

Antibacterial prophylaxis is generally not recommended for neutropenic patients undergoing chemotherapy. Two studies in the Sept. 8 issue of the *New England Journal of Medicine* may change that recommendation. The first study from Italy looked at 760 adult patients who were undergoing treatment for acute leukemia, solid tumors, or lymphoma and were at risk for chemotherapy-induced neutropenia lasting more than 7 days. Many were undergoing stem cell transplantation. Patients were randomized received either oral levofloxacin 500 mg daily or placebo from the start of chemotherapy until the resolution of neutropenia. The rate of fever present for the duration of neutropenia was reduced in the levofloxacin group (65% levofloxacin prophylaxis, 85% placebo; RR, 0.76, 95% CI; $P = 0.001$). The levofloxacin group also had a lower rate of microbiologically documented infections (17% absolute difference in risk; $P < 0.001$), bacteremia (16% absolute difference in risk; $P < 0.001$), and single agent gram-negative bacteremias (7% absolute difference in risk; $P < 0.01$), compared to the placebo group. There was no difference in mortality, and there was no difference in outcomes between patients with acute leukemia or those with solid tumors or lymphoma. Treatment was generally well-tolerated. The authors conclude that prophylactic treatment with levofloxacin is an effective and well-tolerated way of preventing febrile episodes and other relevant infection-related outcomes in patients with cancer and profound and protracted neutropenia (Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia. *N Engl J Med*. 2005;353:977-987).

The second study from England looked at 1565 patients undergoing cyclic chemotherapy for solid tumors or lymphoma who were at risk for temporary, severe neutropenia. Since these patients were receiving cyclic chemotherapy, the rate of neutropenia was significantly lower than the first study. Patients were randomized to receive levofloxacin 500 mg daily or placebo for 7 days during the expected neutropenia period. During the first cycle of chemotherapy, 3.5% of patients in the levofloxacin group had a least one febrile episode, compared with 7.9% in the placebo group ($P < 0.001$). During the entire chemotherapy course, 10.8% of patients in the levofloxacin group had a least one febrile episode, compared with 15.2% of patients in the placebo group ($P = 0$ .01); the rate of probable infection was 34.2% and 41.5%, respectively ($P = 0.004$). Hospitalization rates were significantly higher in the placebo group, and the rate of severe infection was twice as high in the placebo group (1.0% vs 2.0% [$P = 0$ .15]). The death rate was same in both groups. The authors concluded that prophylactic use of levofloxacin reduces the rate of fever, probable infection, and hospitalization (Cullen M, et al. Antibacterial Prophylaxis After Chemotherapy for

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

Solid Tumors and Lymphomas. *N Engl J Med*. 2005;353:988-998).

An accompanying editorial suggests that these are important studies which provide more data on prophylactic antibiotics in neutropenia that had previously been available. However, further study still needs to define which patients are at highest risk and the period of greatest risk during chemotherapy. Most importantly, the emergence of resistant organisms, which was seen in the Italian study, is a major concern. The author states "If prophylactic antimicrobial therapy is to be adopted at a cancer center, it should be accompanied by vigorous infection-control practices and careful monitoring for the emergence of resistant organisms" (Baden LR. Prophylactic Antimicrobial Agents and the Importance of Fitness. *N Engl J Med*. 2005:353: 1052-1054).

Is It Hot In Here?

Hot flashes are common problem for women undergoing treatment for breast cancer. A new study suggests that gabapentin adjusted 900 mg per day may help alleviate symptoms. Four hundred twenty women, with breast cancer and 2 or more hot flashes per day, were randomly assigned to receive gabapentin 300 mg per day or gabapentin 900 mg/day or placebo in 3 divided doses for 8 weeks. The 900 mg per day does reduce hot flashes by 49% and 46% at 4 and 8 weeks, respectively. The 300 mg dose was not effective at a statistical level. The authors suggest that gabapentin 900 mg per day should be considered for treatment of hot flashes in women with breast cancer (Pandya KJ, et al. Gabapentin for Hot Flashes in 420 Women with Breast Cancer: A Randomised Double-Blind Placebo-Controlled Trial. *Lancet*. 2005;366:818-824).

Homeopathy vs Conventional Medicine

A new study suggests that homeopathy is no better than placebo in treating disease. Researchers from the University of Berne in Switzerland, reviewed over 100 clinical trials of homeopathy and conventional medicine. Eight large homeopathy trials were eventually used in a meta-analysis, along with 6 large conventional medicine trials. The odds ratio for homeopathy was 0.88 and for conventional medicine 0.58. When only the largest trials were used, the odds ratio for homeopathy was 0.96 and for conventional medicine 0.67. This suggests that the benefit from homeopathy is no better than random chance (Shang A, et al. Are the Clinical Effects of Homeopathy Placebo Effects? Comparative Study of Placebo-Controlled Trials of Homeopathy and Allopathy. *Lancet*. 2005; 366: 726-732). An accompanying editorial states "Now doctors need to be bold and honest with their patients about homeopathy's lack of benefit. . ." (The End of Homeopathy. *Lancet*. 2005;366:690). Homeopathy which uses very dilute solutions to treat disease has been popular in Europe; however, this study marks a trend away from homeopathy in England. The Swiss government also recently withdrew insurance coverage for homeopathy after a 5-year trial because it did not meet efficacy and cost effectiveness criteria.

FDA Actions

The FDA has approved a new 4-component vaccine for children aged 12 months to 12 years that includes measles, mumps, rubella, and varicella viruses. The approval was based on data showing effectiveness of the vaccine was similar to that of MMR (measles, mumps, and rubella) and varicella vaccine (Varivax). The new vaccine will be marketed under the trade name ProQuad by Merck & Co.

Sanofi-Synthelabo has received approval to market an extended release formulation of zolpidem (Ambien) for the treatment of insomnia. The new preparation is a bi-layered tablet that delivers the drug in 2 stages, a quick dissolving layer to induce sleep, and a slower release layer to provide sleep continuity. Ambien CR will be marketed in a 12.5 mg dose for adults and a 6.25 mg strength for patients 65 years and older.

The Senate has approved a bill to limit over-the-counter sales of pseudoephedrine, a key ingredient in the illicit manufacturing of methamphetamine. The bill which has bipartisan support, will require decongestant medications containing pseudoephedrine to be sold behind pharmacy counters and would limit how much any individual can buy to 7.5g a month (250 30 mg tablets).The bill also encourages a computer tracking system to limit multiple purchases at different stores and pharmacies. A similar bill is working its way to the House of Representatives.

The FDA is one step closer to approving Pfizer's inhaled insulin powder after an advisory panel voted 7-2 to urge approval. The preparation, which will be marketed under the trade name Exubera, is a short-acting insulin powder that is used before meals. The drug does not replace the need for long acting insulin injections. There have been concerns that Exubera may hamper lung function in diabetics, but Pfizer has been able to show 2-year data that suggest patients experience only minimal decrease in lung capacity that is reversible if the drug is stopped. ■