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INSIDE

CME Evaluation Enclosed

Bevacizumab with Gemcitabine Shows Activity in Phase II Pancreatic Cancer Trial

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a phase II trial of bevacizumab and gemcitabine in patients with advanced pancreatic cancer, responses were observed in 21% and stable disease in 46%. Although the median overall survival was not dramatically superior to that reported for gemcitabine alone, there is rationale for proceeding to larger scale phase III trial of this combination.*

Source: Kindler HL, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2005;23:8033-8040.

KINDLER AND COLLEAGUES COORDINATED A MULTI-CENTER phase II trial of bevacizumab given in combination with gemcitabine for patients with previously untreated advanced pancreatic cancer. The goals of the study were to determine the objective tumor response rate, overall and progression-free survival rates and toxicity profile of this combination.

Fifty-two patients were enrolled at 7 centers between November 2001 and March 2004 and were treated with gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. All patients also received bevacizumab (Avastin®, Genentech, South San Francisco, CA) 10 mg/kg on days 1 and 15, after the gemcitabine infusion.

Of the 52 patients, 11 (21%) had confirmed partial responses and 24 (46%) had stable disease. The 6-month survival rate was 77%, the median survival was 8.8 months, and the median progression-free survival was 5.4 months. Pretreatment plasma VEGF levels did not correlate with outcome. Grade 3 and 4 toxicities included hypertension in 19%, thrombosis in 13%, visceral perforation in 8%, and bleeding in 2%.

Detailed in the current paper are a relatively high occurrence of toxicities, although most of which did not reach grade 3. For exam-

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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.

ple, 44% developed hypertension, but this reached grade 3 in just 19% (and none experienced hypertensive crisis). Similarly, proteinuria occurred in 36% of patients, but was grade 3 in only 2% and bleeding episodes occurred in 31% (epistaxis in 23%), but severe bleeding occurred only in one patient.

The investigators concluded that this combination (gemcitabine and bevacizumab) and schedule was sufficiently positive with regard to clinical outcomes to warrant additional, larger-scale investigation.

COMMENTARY

The treatment of pancreatic cancer remains disappointing. Although in phase II trials, the addition of second agents (eg, 5 fluorouracil, oxaliplatin, cisplatin, and others) have shown promise, in larger Phase III trials, the combinations have shown no advantage over gemcitabine alone.[1-3] In the current trial, bevacizumab was tested in combination with gemcitabine in patients with previously untreated pancreatic cancer. Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), which has been shown to promote the growth and spread of a number of human tumors, including pancreatic cancer.[4] The rationale for this trial was strengthened by the observations that pancreatic cells grown in culture were stimulated by VEGF[5] and inhibitors of VEGF reduced angiogenesis and tumor growth in animal models of pancreatic cancer.[6] Thus, the current trial has great appeal, for the utilization of bevacizumab is based upon solid rationale and the treatment directed at a population distinctly in need of a therapeutic breakthrough. The results, although modest by phase II standards, are sufficient to warrant a larger scale investigation and it is gratifying to see that the Cancer and Leukemia Group B has undertaken such a trial comparing gemcitabine plus bevacizumab vs gemcitabine plus placebo. Until the findings are reported, however, it would seem the risks and expense may not warrant incorporation into community standard practice. ■

References

1. Berlin JD, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol*. 2002;20:3270-3275.
2. Rocha Lima CM, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol*. 2004;22:3776-3783.
3. Louvet C, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. 2005;23:3509-3516.
4. Korc M. Pathways for aberrant angiogenesis in pancreatic cancer. *Mol Cancer*. 2003;2:8.
5. Itakura J, et al. Concomitant over-expression of vascular endothelial growth factor and its receptors in pancreatic cancer. *Int J Cancer*. 2000;85:27-34.

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6. Baker CH. Blockade of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling for therapy of metastatic human pancreatic cancer. *Cancer Res*. 2002;62:1996-2003.

Heparin-Induced Thrombocytopenia with Low Molecular Weight Heparin

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Section of Hematology/Oncology, University of Chicago

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

Synopsis: *In this prospective study of 1754 medical patients receiving low molecular weight heparin (LMWH), Prandoni and colleagues found a 0.8% incidence of heparin induced thrombocytopenia. The incidence was similar to a prior study they performed in medical patients receiving unfractionated heparin (UFH). Prior heparin exposure was associated with an increased risk of HIT. These data raise the possibility that HIT occurs more commonly in medical patients than previously appreciated and the incidence may not necessarily be significantly lower than with UFH. Clinicians must remain aware of the possibility of HIT, even in patients receiving either LMWH or UFH.*

Source: Prandoni P, et al. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. *Blood*. 2005;106:3049-3054.

Heparin-induced thrombocytopenia (HIT) is a life-threatening immune complication related to heparin exposure, especially unfractionated heparin (UFH). The syndrome is characterized by falling platelet counts and a paradoxical proclivity toward thrombosis. It usually occurs 5 days or more after heparin exposure although HIT may develop sooner in patients with recent heparin exposure. The incidence has been shown to be significantly lower with the use of low molecular weight heparin (LMWH). In a randomized controlled study, only 1/720 (0.1%) patients treated with LMWH developed HIT compared to 8/356 (2.2%) receiving UFH. The low incidence of HIT with LMWH has raised questions whether patients on LWMH require surveillance for HIT.

Prandoni and investigators report a large prospective study of medical patients receiving LMWH for thrombosis prophylaxis and treatment and report the incidence of HIT. In this multicenter trial, the 1754 evaluable patients were followed platelet counts, serology for heparin induced antibodies, and clinical events.

Twenty-one percent received prophylaxis LMWH and the remainder received either intermediate/fixed dosing or therapeutic doses. Prior exposure to UFH or MWH was present in 34%. Twenty-nine patients had an unexpected decline of > 50% in platelets not accounted for by other factors but only 14/29 tested positive for heparin-induced antibodies. The incidence of HIT was 0.8% (14/1754; 95% CI, 0.31-1.12%). There was no difference in incidence of those receiving LMWH for prophylaxis compared to treatment LMWH. The incidence was 1.7% among those with prior heparin exposure. Most patients received anticoagulation for HIT but 4/14 developed symptomatic thrombosis.

COMMENTARY

LMWH has found widespread use as an UFH substitute for both thrombosis prophylaxis and treatment owing to equal or superior efficacy and reduced need for monitoring. Another potential benefit of LMWH has been the significantly lower incidence of one of the most serious complications of UFH—heparin-induced thrombocytopenia. Limited data has addressed the incidence of HIT in medical patients. From a clinical perspective, HIT, either recognized or undiagnosed, often leads to consultation by a hematologist/oncologist.

In a prior study by the same group using UFH, a very similar incidence of HIT of 0.84% was found compared to the 0.8% incidence detected her with LMWH. While one can not draw definitive conclusions in non-randomized studies, the findings are intriguing and contradict prior work suggesting a much lower incidence of HIT with LMWH. The data imply HIT may occur more commonly in medical patients than previously appreciated. Although a 0.8% incidence is low, the serious ramifications of a missed diagnosis raise concerns about whether routine platelet monitoring may be needed for patients receiving LMWH, especially in the first two weeks of therapy. The increased incidence in patients with prior exposure may point to a group where a high index of suspicion is warranted. ■

References

1. Lindhoff-Last E, et al. Incidence and clinical relevance of heparin-induced antibodies in patients with deep vein thrombosis treated with unfractionated or low-molecular-weight heparin. *Br J Haematol*. 2002;118:1137-1142.

Routine Surgical Staging in Grade 1 Endometrial Cancer Appears Beneficial

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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M.D. Anderson Cancer Center, Houston TX
Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol Myers-Squibb, and Ortho Biotech.

Synopsis: *Surgical staging in patients presenting with grade 1 endometrial cancer significantly impacted postoperative treatment decisions in 29% of patients. Omitting lymphadenectomy in patients presenting with grade 1 endometrial cancer may lead to inappropriate postoperative management.*

Source: Ben-Shachar I, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. *Obstet Gynecol*. 2005;105:487-493.

Endometrial cancer is the most common gynecologic malignancy and is usually characterized by limited disease at presentation. Among the number of known prognostic factors, grade of disease is one frequently used to triage patients for formal surgical staging. Ben-Shachar and colleagues address the clinicopathological features and treatment recommendations of well-differentiated (grade 1) endometrial cancer in a retrospective review of surgically staged patients. Over a 6.5-year period, 181 patients were identified with preoperative grade 1 endometrial cancer. Whether defined by endometrial biopsy or dilation and curettage, all patients underwent formal surgical staging including pelvic and para-aortic lymphatic dissection, cytology and for intraoperatively identified high-risk histology, intraperitoneal biopsies or debulking. Final histology of grade 1 was seen in 81% of patients with no difference identified between the preoperative sampling techniques. Two patients with grade 1 preoperative sampling were found intraoperatively to have sarcoma.

In all, half of the patients were found with non-invasive disease. The remainder had myometrial invasion (33%), cervical extension (7%), adnexal metastases or positive cytology (4%), nodal spread (4%), or intra-abdominal spread (3%). Based on commonly used criteria for surgical staging (grade 1-2 with depth of invasion > 50%, grade 3, cervical extension, high-risk histology), 26% of these grade 1 lesions would have warranted complete staging. Importantly, more than half of these of patients (n = 30/54) with high-risk uterine features required no further therapy based on their surgical findings. Overall, 29% of grade I patients (12% treated and 17% untreated) were benefited by information gained by formal surgical staging. Ben-Shachar et al conclude that even this apparent "low-risk" group of patients requires formal surgical evaluation for treatment precision.

COMMENTARY

Following a series of prospective clinico-pathological observational studies, FIGO, in 1988, changed the staging schema of uterine cancer from one derived from preoperative clinical findings to one based on surgical evaluation of the uterine and extra-uterine sites as well as grade. Appropriate assignment of stage now requires resection of the uterus, evaluation of peritoneal cytology, retroperitoneal node evaluation and peritoneal inspection. The immediate implication from this new classification algorithm was that specialized and directed surgical biopsy is needed to provide information that more accurately describes the distribution of disease. While the principal goal of staging is to facilitate communication among physicians and patients regarding a designated disease status, the allocation of a particular stage is often used for treatment triage and in many cases, has prognostic implications. A check on surgical staging in a 1996 report revealed that less than a third of newly diagnosed endometrial patients were undergoing staging procedures.[1] While likely increased today, there is still a prevailing bias that the earliest lesions (grade 1) don't carry enough risk to warrant routine formal surgical staging. This is the principal focus of the current paper by Ben-Shachar et al.

Precision of treatment in this disease implies that those who need adjuvant treatment get it and those who don't, don't get it. For instance, 20 patients with grade I tumors were found with nodal or intraperitoneal metastases, including 4 in whom no other clues to its presence (depth of invasion or higher grade tumor) were apparent. In addition, 30 patients with high-risk uterine features but without metastases were not treated after surgical staging. This mirrors the results of a survey of gynecologic oncologists who would recommend adjuvant therapy based on whether surgical staging data were available. In nearly every category of grade and depth of invasion, a significant "overuse" of adjuvant therapy would be recommended in the absence of surgical staging data.[2] Further, some investigators have advocated complete lymphadenectomy as a therapeutic maneuver in patients with uterine cancer.[3] However, study limitations such as

patient selection bias have made this a controversial topic. Fortunately, the merits of this procedure are being evaluated in a prospective randomized trial (MRC-ASTEC trial).[4]

The case for routine surgical staging in medically fit patients is usually counterbalanced by concerns of morbidity and simple availability. Although, experience from prospective randomized trials and retrospective series suggests the morbidity is low, there is little solution for those patients treated in areas where gynecologic oncology expertise is unavailable. Knowledge of staging procedures by the gynecologist can aid other surgeons if called upon to provide the needed samplings. In this regard, an important distinction should be made for high-risk histology (eg, papillary serous), where intraperitoneal spread rates, even among apparent stage I patients, occurs sufficiently high enough to warrant intraperitoneal staging similar to ovarian cancer.[5]

There's little controversy that patients with grade 1 lesions are most likely to have the most favorable uterine findings. However, utilizing that rule of thumb to plan surgical management overlooks more than a quarter of patients who would benefit from formal evaluation. Whether that is accomplished by patient referral or co-management with gynecologic oncology is immaterial as long as the appropriate data are retrieved.[6] ■

References

1. Partridge EE, et al. The National Cancer Data Base report on endometrial cancer. *J Surg Oncol*. 1996;61:111-123.
2. Naumann RW, et al. The use of adjuvant radiation therapy by members of the Society of Gynecologic Oncologists. *Gynecol Oncol*. 1999;75:4-9.
3. Seago DP, et al. Potential benefit of lymphadenectomy for the treatment of node-negative locally advanced uterine cancers. *Gynecol Oncol*. 2001;83:282-285.
4. Creutzberg CL, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. *J Clin Oncol*. 2004;22:1234-1241.
5. Slomovitz BM, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. *Gynecol Oncol*. 2003;91:463-469.
6. Pearl ML, et al. Outcomes of endometrial cancer patients undergoing surgery with gynecologic oncology involvement. *Obstet Gynecol*. 2002;100:724-729.

Randomized Trial First to Demonstrate a Survival Benefit in Patients with Recurrent Cervical Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *Despite increased toxicity, CT did not significantly reduce patient QOL when compared with cisplatin alone. Patient-reported QOL measures may be an important prognostic tool in advanced cervix cancer*

Source: Long HJ, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2005. 23:4626-4633.

Cisplatin has long been considered the standard first-line chemotherapy of choice for cervical cancer patients demonstrating disease recurrence. A series of randomized trials has established that 1) higher doses of this agent are not associated with longer survival but are associated with higher toxicity and 2) cisplatin-based combinations (to date) can increase response and progression-free survival, but without increasing overall survival, and at the expense of significant toxicity. As such, single-agent cisplatin has remained the benchmark for efficacy trials. Under these conditions, Long and colleagues conducted a randomized clinical trial to evaluate 2 promising cisplatin- based combinations (topotecan/cisplatin and methotrexate, vinblastine, doxorubicin, cisplatin [MVAC]) against standard single-agent cisplatin in recurrent cervix cancer patients with measurable disease. Overall survival was the primary end point. Three hundred fifty-seven patients were enrolled and randomized. Treatment-related mortalities in 4 of 63 patients randomized to MVAC prompted closure of this arm to further accrual. The remaining 294 patients were randomized to either cisplatin or cisplatin/topotecan. Nearly 60% of enrolled patients had previously received cisplatin-based chemoradiation as therapy for their primary disease. Toxicity, particularly hematologic, was significantly higher for the cisplatin/topotecan arm. Significant treatment-related infection was also higher in the combination arm. However, both progression-free and overall survivals were significantly longer for the combination. The hazard for progres-

sion and death was reduced 26% and 23%, respectively, relative to single agent cisplatin. The absolute differences in median progression-free and overall survival were 1.7 mos and 2.9 mos, respectively. In addition, objective response to therapy doubled (13% to 27%), a statistical improvement. Two patient characteristic factors were identified as important in the interpretation of these results: 1) previous exposure to platinum as chemoradiation, and 2) disease-free survival until recurrence. Both were found to be significant prognosticators of response to subsequent treatment; patients not previously exposed to platinum as a radio-sensitizer and those presenting with a long progression-free interval were most likely to benefit from cisplatin/topotecan. Long and colleagues concluded that the combination was more efficacious than single agent cisplatin. This trial is the first to demonstrate an overall survival advantage for any combination over cisplatin.

COMMENTARY

Effective therapy for recurrent cervix cancer remains a significant challenge—one in which very little progress has been made over the last 20 years despite an expansion of new chemotherapeutics. Patients recurring after primary surgical treatment may have a curative radiotherapy option if the disease is localized. However, most, including those who have received radiotherapy as primary treatment or as an adjuvant to surgery, have disease that encompasses a mixture of regional and distant sites not amenable to curative radical resection. The natural history of this recurrence is one of progression, and most patients discovered with disease recurrence succumb to their disease in short order. Since effective systemic strategies have not been identified, it is not surprising that our experience with randomized chemotherapy trials is one in which overall survival is not affected by new treatment combinations, despite an improvement in response and progression-free survival. In light of this background, the current study by Long et al is noteworthy and deserves our attention.

A key benefit of phase III investigation is that the effects known and unknown, which could positively or negatively affect one's primary objectives, are balanced by the randomization process. In the study of recurrent cervical cancer therapy, this is not a trivial point. We and others have demonstrated that the location of recurrence alone can affect the likelihood of response 2-fold.[1,2] Patients with "in-the-radiated-field" recurrences are much less likely to achieve tumoricidal doses of chemotherapy and fair much worse than those with distant site recurrences.

Table

Randomized GOG Trials in Recurrent Cervix Cancer

Study	Response	PFS	OS
GOG-043	+	-	-
GOG-110	+	+	-
GOG-149	-	-	-
GOG-169	+	+	-
GOG-179, Current Study	+	+	+

KEY

PFS: Progression-free survival; OS: Overall survival

GOG-043: Cisplatin 50 mg/m^2 vs Cisplatin 20 mg/m^2/day × 5 vs Cisplatin 100 mg/m^2

GOG-110: Cisplatin vs Cisplatin/Mitolactol vs Cisplatin/Ifosfamide

GOG-149: Cisplatin/Ifosfamide vs Cisplatin/Ifosfamide/Bleomycin

GOG-169: Cisplatin vs Cisplatin/Paclitaxel

In addition, many exploratory trials of new chemotherapeutic include patients who have advanced, but previously untreated disease and of varying performance status. Nonetheless, trials such as these provide new candidates for the phase III investigation where the standard of care is tested.

Since the discovery of cisplatin and the demonstration of its activity in cervix cancer, the agent has been a staple of therapy. Within the GOG, successive clinical trials have addressed quantity of drug, schedule and various platinum combinations (*see Table*). Prior to the current study, the overwhelming consensus has been that "more is not better." However, the results of the current trial call this mantra into question and have renewed interest in exploring novel combinations against the likely new standard. Indeed, the recently opened follow-up clinical trial is studying paclitaxel, vinorelbine and gemcitabine platinum doublets against cisplatin/topotecan. However, accompanying more therapy is more toxicity; for those with short life expectancies this is a major consideration and has largely been responsible for keeping the single agent as standard despite gains in intermediate end points such as response and progression-free survival. To better understand the nature and degree to which toxicity affects enrolled patients in balance with their response to therapy, sophisticated quality of life (QoL) measures have were developed and administered in this trial. In an accompanying article regarding the QoL in this study, Monk and colleagues demonstrated that despite the increased toxicity, QoL did not decrease either on therapy or following treatment conclusion.[3] Taken as a whole, the

combination appears a good candidate to replace the current standard.

In the bigger picture, the gains made, though significant, are still too small and should not be satisfactory to either patients or clinicians. Better strategies are needed such as disruptors of angiogenesis and/or cell signaling. Our search needs to continue if real progress is to be made in this disease. ■

References

1. Brader KR, et al. Chemotherapy for cervical carcinoma: factors determining response and implications for clinical trial design. *J Clin Oncol*. 1998;16:1879-1884.
2. Zanetta G, et al. Factors predicting response to chemotherapy and survival in patients with metastatic or recurrent squamous cell cervical carcinoma: a multivariate analysis. *Gynecol Oncol*. 1995;58:58-63.
3. Monk BJ, et al. Quality of Life Outcomes From a Randomized Phase III Trial of Cisplatin With or Without Topotecan in Advanced Carcinoma of the Cervix: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2005. Jun 6;[Epub ahead of print].

Proteomic Profiling in Ovarian Cancer: Is it Plausible?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *The reproducibility of the proteomic profiling approach has yet to be established.*

Source: Baggerly KA, et al. Signal in noise: evaluating reported reproducibility of serum proteomic tests for ovarian cancer.*J Natl Cancer Inst*. 2005;97:307-309.

Reproducibility of complex proteomic signatures in detecting early stage ovarian cancer has proven to be a significant challenge in the field of biomarker discovery. Although early reports of proteomic profiling demonstrated near 100% sensitivity and specificity in discriminating ovarian cancer from non-cancer, the ability to reproduce these results across datasets has been difficult. Baggerly and colleagues examined 2 proteomic spectral datasets available in the public domain with the intent of testing the published classification method and assessing reproducibility. They then calculated the probability that classification could occur by chance alone. Using statistical methodology similar to the original reports then followed by random allocation of spectral clusters, Baggerly et al report that the predictive spectral peaks were less accurate (less than 80%) than originally reported. Applying a separate methodology (jack-knife approach) to test the original peaks to a second dataset produced high accuracy (98.4%). However, this level of accuracy was met or exceeded in 6% of the simulations using completely random values. On the basis of these 2 findings, Baggerly et al concluded that proteomic signature profiling to accurately and reproducibly discriminate cancer from non-cancer was not plausible and may be the effect of procedural bias.

■ COMMENTARY

News of accurate discrimination of cancer patients from unaffected patients via evaluation of blood samples was a welcomed and widely publicized advance in the field of ovarian cancer screening research. Although difficult to understand, the technology of developing and interpreting proteomic signatures from banked blood of both cancer patients, patients with non-cancerous lesions, and normal controls, appeared to offer renewed hope in the ability to accurately classify patients with disease, particularly those with early stage disease where survival is the best. While the data being produced were patterns (spectral peaks) recognizable only by sophisticated statistical algorithms sensitivity, specificity and accuracy were very high and far better than our best (and current) biomarker methodology. However, almost as soon as the data were reported, news of the inability to accurately reproduce the data permeated the clinical community who were already baited with the promise of a commercial product awaiting approval. The current report, on the surface, seems to dampen that enthusiasm even more where the results of 2 independent data sets were found to not be reproducible and could be explained by chance—that is by overfitting. Overfitting errors are encountered when a multivariate model is used to fit a very large number of possible predictors. Indeed, Baggerly et al demonstrated that simply choosing random spectral peak values for a prediction model met or exceeding the predictive accuracy of the historical model in 6% of their samplings. This would imply that the plausibility for prediction based on the public domain datasets was low and confounded.

The Baggerly article is followed by 2 commentaries in the *Journal of the National Cancer Institute* that help to put this apparent conundrum into perspective.[1] We find from the original authors of one of the sentinel articles that the datasets placed into the public domain were generated from experimental settings where one or more

parameters were purposefully altered to study the effects on output spectra. In this situation, the datasets would likely not be reproducible as the baseline between sets is intentionally and artificially adjusted. In addition, it was raised that issues of reproducibility are premature as the technology is a moving target and continuously updated. However, as is discussed in the second commentary, reproducibility is the lifeblood of moving this complex promising field (termed "-omics") forward. It is further complicated by the dichotomy of discovery; on the one hand, you have a test based on pattern recognition alone, where the results are based on unknown and undescribed proteins, and on the other, you have biomarkers development, which would take on the tedious process of describing these proteins, showing their relevance (biological impact) to ovarian cancer and then develop a measurable antibody in the patient's sera. Calls for a new trial have been made, where reproducibility is the mission, in a single data set with careful attention to statistical methodology.[2,3]

What is clear from the 10 pages of commentary that accompanies the 3-page brief communication is that this field holds tremendous promise in promoting our ability to identify "at-risk" patients, but must be embarked upon carefully. In addition, free interchange and discussion through publicly disseminated data will help perfect this important task. ■

References

1. Ransohoff DF. Lessons from controversy: ovarian cancer screening and serum proteomics. *J Natl Cancer Inst*. 2005;97:315-319.
2. Zhang Z, et al. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. *Cancer Res*. 2004;64:5882-5890.
3. Zhu W, et al. Detection of cancer-specific markers amid massive mass spectral data. *Proc Natl Acad Sci USA*. 2003;100:14666-14671.

CME Questions

16. Gemcitabine plus bevacizumab was shown in a phase II trial to:

a. have intolerable toxicity.
b. have high rates of toxic reactions, but mostly low grade.
c. have no toxicity beyond what is expected for gemcitabine as a single agent.
d. produce hypertensive crisis in 23%.

17. Which of the following is true regarding heparin-induced thrombocytopenia?

a. Never occurs with low-molecular heparin
b. Can lead to life-threatening thrombosis
c. Only occurs in patients with prior heparin exposure
d. Can only be diagnosed on autopsy

Answers: 16 (b); 17 (b)

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Beta-Blockers Therapy for the Treatment of Hypertension

Beta-blockers should not be recommended as first-line therapy for hypertension in patients without heart disease, according to a new study. Researchers from Sweden performed a meta-analysis on 13 randomized controlled trials comparing treatment with beta-blockers with other antihypertensive drugs. Seven other studies were reviewed in which beta-blockers were compared with placebo or no treatment. The relative risk of stroke was 16% higher for patients who were treated with beta-blockers (95% CI, 4-30%) compared to other drugs. Beta-blockers reduced the relative risk of stroke by 19% compared to no treatment or placebo; however, this was about half the reduction expected from previous hypertension trials. There was no difference seen in the rates of myocardial infarction or overall mortality. A possible mechanism for these findings is that beta-blockers reduce brachial blood pressure out of proportion to central blood pressure compared with other antihypertensives.

The authors suggest that beta-blockers are less effective than other antihypertensive drugs in preventing stroke, and should not be a first choice in the treatment of primary hypertension (Lindholm LH, et al. Should Beta Blockers Remain First Choice in the Treatment of Primary Hypertension? A Meta-Analysis. *Lancet*. 2005;366:1545-1553). This same group published a study in 2004, suggesting that atenalol was a poor choice for treatment of hypertension (Carlberg B, et al. Atenolol in Hypertension: Is It Wise?*Lancet*. 2004;364:1684-1689). An accompanying editorial states "Surely, therefore, the era of beta-blockers for hypertension is over," but suggests that these drugs should not be discontinued abruptly, and should be discontinued with extreme caution in patients with coronary artery disease (Beever DG, et al. The End of Beta Blockers for Uncomplicated Hypertension? *Lancet*. 2005;366:1510-1512).

Treatments for Acute Migraine

Two studies in the September issue of the Journal of Headache find that sumatriptan alone is inferior to other treatments for acute migraine. In the first study, 972 migraine patients were randomized to treatment with sumatriptan 50 mg, naproxen sodium 500 mg, sumatriptan 50 mg plus naproxen 500 mg, or placebo at the onset of headache symptoms. The sumatriptan plus naproxen group fared the best, with 46% of subjects achieving a 24-hour pain relief response. Sumatriptan alone resulted in 29% of patients achieving the same result, while naproxen alone resulted in the 25% response, and placebo resulted in a 17% response ($P < .001$). Relief of pain at 2 hours was achieved in 65% of the combination group, 49% of the sumatriptan patients, 46% of naproxen patients, and 27% of placebo patients ($P < .001$). The incidence of recurrent headache 24 hours later was also lowest in the sumatriptan plus naproxen group. Other migraine symptoms, includ-

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ing nausea, photophobia, and phonophobia were also most effectively treated with sumatriptan plus naproxen. Adverse effects were similar in all the treatment groups (Smith TR, et al. Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine. *Headache*. 2005;45:983-991). In the second study, sumatriptan was compared with acetaminophen-aspirin-caffeine (AAC) in the early treatment of migraine. In a randomized, controlled clinical trial, 171 patients took either sumatriptan 50 mg or AAC (acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg [Excedrin Extract Strength 2 tabs], or Excedrin Migraine 2 tabs at the first sign of a migraine attack. AAC was significantly more effective ($P > .05$) than sumatriptan in the early treatment of migraine, as shown by superiority and summed pain intensity difference, pain relief, pain intensity difference, response, sustained response, relief of assisted symptoms, use of rescue medications, disability relief, and global assessments of effectiveness (Goldstein J, et al. Acetaminophen, Aspirin, and Caffeine Versus Sumatriptan Succinate in the Early Treatment of Migraine: Results From the ASSET Trial. *Headache*. 2005;45:973-982).

Statin Therapy for ACS Patients

Early aggressive statin therapy is beneficial for patients with acute coronary syndrome (ACS), according to a new study. In a continuation of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT -TIMI 22) trial, the timing of intensive statin therapy was evaluated in patients with acute coronary syndrome. A total of 4162 patients with ACS were randomized to intensive statin therapy with atorvastatin 80 mg or standard therapy with pravastatin 40 mg. The composite end points of death, MI, or rehospitalization for recurrent ACS were determined for each group at 30 days. ACS patients who were started in the hospital on intensive statin therapy fared better than those with standard therapy (composite end point at 30 days 3% intensive therapy vs 4.2% standard therapy [HR = 0 .72; 95% CI, 0.52 to 0.99; $P = .046$]). The authors conclude that ACS patients should be started on aggressive statin therapy in the hospital and continued long-term (Ray KK, et al. Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes: Results from the PROVE IT-TIMI 22 Trial. *J Am Coll Cardiol*. 2005;46:1405-1410). In another follow-up from the PROVE IT-TIMI 22 study in the same Journal, researchers looked at whether very low LDL levels from aggressive statin therapy are associated with adverse effects. Thirty-one percent of patients treated with atorvastatin achieved LDL levels between 80 and 60mg/dL, with another 34% between 60 and 40 mg/dL, and 11% less than 40 mg/dL. There were no significant differences in safety parameters, including muscle, liver, or retinal abnormalities, intracranial hemorrhage, or death in the very low LDL groups. Patients with LDL levels less than 60 had fewer major cardiac events, including death MI and stroke. The authors conclude that very low LDL levels are not associated with adverse effects, and appear to be associated with fewer adverse cardiovascular outcomes (Wiviott SD, et al. Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy: A PROVE IT-TIMI 22 Substudy. *J Am Coll Cardiol*. 2005;46:1411-1416).

The Correct Dosing for Onychomycosis

Many physicians have prescribed terbinafine in a pulse-dosing regimen of 2 pills per day for one week, one week a month, for 3 to 4 months for the treatment of onychomycosis. The regimen is thought to increase compliance, as well as reduce cost. Pulse dosing however is not an approved therapy, and now a new study suggests that it is not as effective as once daily dosing.

The study recruited 306 volunteers with onychomycosis, involving at least 25% of the toenail. Patients were randomized to terbinafine 250 mg daily for 3 months or terbinafine 500 mg daily for one week per month for 3 months. Mycological cures were higher with once-a-day dosing (71% vs 58.7%; $P = .03$). Clinical cures were also higher with once-a-day dosing (44.6% vs 29.4%; $P = .007$), as were complete cures of target toenail (40.5% vs 28.0%; $P = .02$), and complete cure of all 10 toenails (25.2% vs 14.7%; $P = .03$). Tolerability of the regimens did not differ significantly between groups.

The authors conclude that once daily dosing appears to be superior to pulse dosing, however, they also found "this expensive therapy to me much less effective than previously believed, particular for achieving complete cure of all 10 toenails" (Warshaw EM, et al. Pulse Versus Continuous Terbinafine for Onychomycosis: A Randomized, Double-Blind, Controlled Trial. *J Am Acad Dermatol*. 2005;53:578-584).

FDA Actions

The FDA has approved the once-a-day oral iron chelator for the treatment of chronic iron overload due to blood transfusions. Novartis will market deferasirox (Exjade) as an oral alternative to intravenous chelating agents. ■