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INSIDE

Predictors of Response to Gefitinib (Iressa®)

ABSTRACT & COMMENTARY

Synopsis: *Gefitinib, an inhibitor of EGFR tyrosine kinase, has been demonstrated to produce clinical responses in a small number of patients with advanced non-small-cell lung cancer. Prior reviews had indicated that women and patients with adenocarcinoma histology had a somewhat higher response rate. In this review of 3 consecutive phase II trials, other clinical features were sought that might predict treatment response. Multivariable analysis revealed the presence of bronchioalveolar features and being a never smoker were additional, independent predictors of response.*

Source: Miller VA, et al. *J Clin Oncol*. 2004;22:1103-1109.

Activation of the epidermal growth factor receptor (EGFR) by ligand binding or mutation stimulates cell growth, proliferation, invasion, and metastasis and prevents apoptosis.[1] Inasmuch as EGFR has been shown to be present in all non-small-cell lung cancer (NSCLC) tumors, the receptor itself, or its ligands or downstream effectors have become principal targets in the treatment of these tumors. Theoretically, the inhibition of EGFR and its cellular-mediated effects should retard the growth of NSCLCs driven by EGFR signaling. Gefitinib (Iressa®), a synthetic anilinoquinazoline, inhibits EGFR tyrosine kinase and has been shown to produce radiographic regressions with symptomatic benefits in several phase II trials.[2,3] Clinical and pathologic features including female sex, and adenocarcinoma have been demonstrated to influence response to gefitinib. It has been postulated that additional pretreatment variables may also predict sensitivity to this agent.

Miller and colleagues from the Memorial Sloan-Kettering Cancer Center examined 139 patients with NSCLC participating in 1 of 3 consecutive studies of gefitinib monotherapy. These patients were analyzed for the prognostic significance of stage, sex, age, performance status, bone metastasis, number of prior chemotherapy regimens, use of prior cisplatin, carboplatin or docetaxel, smoking history, and tumor cell type. The latter variables (tumor cell type and smoking history) had not been evaluated in this regard previously.

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Overall, 90% of the 139 patients received 250 mg daily and 2 patients received less than 225 mg daily. The observed response rate to gefitinib in the clinical trials was 15% (95% CI, 9-21%). None of the 38 patients with a NSCLC other than an adenocarcinoma experienced a radiographic regression (0% observed rate; 95% CI, 0-9%; $P < .001$). The adenocarcinoma group was further separated into 2 subgroups—tumors with or without elements of bronchioloalveolar cell carcinoma. The presence of bronchioloalveolar features was found to be significant with regard to treatment (38% vs 14% response rate; $P < .001$). Additionally, 13 (36%) of the 36 never smokers experienced regressions as compared with 8 (8%) of the 104 current or former smokers ($P < .001$). Furthermore, patients with Karnofsky performance status = 80% were more sensitive to gefitinib than those with Karnofsky performance status = 70% (22% vs 8%; $P = .03$). Multivariable analysis demonstrated that the presence of bronchioloalveolar features in an adenocarcinoma (or pure bronchioloalveolar cell carcinoma) and a history of never smoking are independent predictors of gefitinib sensitivity.

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COMMENT BY WILLIAM B. ERSHLER, MD

In previous NSCLC treatment analyses,[2,3] it was apparent that women—and patients with adenocarcinoma—were somewhat more likely to respond to Gefitinib treatment. Now we can add bronchioalveolar features and non-smoking history to those clinical features that would offer predictive value for treatment response. Where we go with these observations remains a question. Should male patients with other histological types of NSCLC be treated with other drugs? Even with lower response rates, prescribing an oral agent that has associated low levels of toxicity certainly deserves some consideration at a time when alternatives are only marginally more successful and have a greater profile of adverse consequences.

Yet, the real hope is that laboratory-oriented investigators will take these clinical observations back to the bench. As indicated by Miller et al, tumor samples from Gefitinib-responding patients will be compared with samples taken from resistant patients by microarray to study the EGFR pathway in an effort to identify molecular markers that might be useful in identifying individual patients likely to respond to gefitinib.

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Results of Interval Debulking Surgery Compared with Primary Debulking Surgery in Advanced-Stage Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Survival rates were similar in patients with advanced-stage ovarian cancer who underwent IDS or PDS. The rates of surgical resection and morbidity were reduced after IDS. IDS can be safely used in unresectable advanced-stage ovarian cancer.*

Source: Morice P, et al. *J Am Coll Surg*. 2003;197(6):955-963.

In an effort to shed light on a controversial approach to advanced ovarian cancer management, Morice and colleagues present intriguing data on the

use of interval debulking surgery following pre-operative chemotherapy. The retrospective study consisted of 2 cohorts, matched for stage, tumor grade, and histology. The first cohort consisted of 57 patients who were determined, largely at surgery, to be unresectable (to less than 2 cm residual disease) by standard debulking techniques. This group received a median 3 courses (range, 2-5) of platinum- and taxane-based chemotherapy followed by a second attempt at cytoreduction. Following this surgery, they were administered a median 5 (range, 3-7) courses of the same chemotherapy. The second cohort—the control group—consisted of 28 patients deemed resectable who underwent standard primary debulking surgery followed by a similar platinum- and taxane-based chemotherapy regimen.

In both cohorts, "optimal" cytoreduction was considered less than 2 cm of residual disease—an achievement made in 84% of the interval debulking surgery group and in 100% of the primary cytoreduction group. Similar rates of complete resection (ie, no gross residual) were achieved in each cohort (51% and 54%, respectively) as well. To document the effects of chemotherapy in the interval-debulking cohort, Morice et al recorded disease volumes in several specific peritoneal and extraperitoneal locations both before and after chemotherapy and compared this disease volume to that found in the control cohort at primary surgery. Following the initial chemotherapy, tumor reduction on specific intra-abdominal structures ranged from 30% on the diaphragmatic peritoneum to 60% on the bowel and rectum regions. In addition, despite the spectrum of disease at entry, the distribution and volume of disease found at cytoreductive surgery was markedly reduced for the interval-debulking group. The rates of bowel resection, large peritoneal, resection and postoperative morbidity were significantly reduced in the interval-debulking group, as well. After adjustment for tumor residual, no significant differences could be determined between the 2 cohorts with regards to disease-free and overall survival. Morice et al conclude that interval-debulking surgery is a viable therapeutic option for patients with unresectable advanced ovarian cancer and is associated with reduced surgical resection and morbidity compared to primary cytoreduction with equivalent survival.

COMMENT BY ROBERT L. COLEMAN, MD

The merits of cytoreductive surgery and chemotherapy for patients with advanced ovarian cancer have been well documented. Typically, the sequence is surgery first and combination platinum- and taxane-based chemotherapy second. In a meta-analysis on the topic of primary cytoreduction, Bristow and colleagues documented that achievement of "optimal" status from surgery was associated with an 11-month (50%) increase in survival compared to "suboptimal" cytoreduction.[1] In addition, each 10% increase in cytoreduction was associated with a 5.5% increase in survival. The result was most notable among institutions and surgeons familiar with the techniques of ovarian cancer resection and goals of debulking. In nearly all studies on this topic, those patients rendered completely disease-free (no gross residual) after primary surgery have the best subsequent performance whether it is reported by intermediate end points such as negative second-look operations and progression-free survival or by durable survival. In an attempt to achieve optimal resection, a variety of surgical techniques and strategies have been reported, such as the radical oophorectomy/posterior exenteration, diaphragmatic resection and stripping, peritoneal implant excision and suprarenal retroperitoneal dissection.[2,3] While these procedures have increased initial cytoreduction rates in some cohorts they have often been associated with increased perioperative morbidity.

An alternative strategy is to "preload" the patient by offering chemotherapy ahead of a cytoreduction attempt. Since ovarian cancer is generally chemosensitive, the strategy has appeal, and most patients will experience a reduction in tumor volume (sometimes elimination of gross disease) before surgery is attempted. The limited number of articles on the topic of neoadjuvant chemotherapy would suggest, as the current article does, that more patients are rendered optimal with less morbidity.[4-7] Unfortunately, there is a confusing assortment of terms that applies to this kind of treatment approach. "Neoadjuvant" chemotherapy, "induction" chemotherapy, and interval cytoreduction have all been used to describe a cohort of patients undergoing chemotherapy ahead of a definitive cytoreduction. To some degree, the disparity in terms may explain the differences seen in clinical trials with respect to survival outcomes. In general, "neoadjuvant" has been used to describe a cohort of patients administered chemotherapy without surgical exploration the diagnosis being determined by cytology or limited biopsy.

Those who have undergone a suboptimal surgical cytoreductive attempt and are to undergo a second exploration are treated with "induction" chemotherapy between the 2 surgeries. Interval cytoreduction, as used in the current study, refers to a cohort of patients undergoing surgical exploration to make the diagnosis and assess cytoreducibility. Chemotherapy is then given prior

to a definitive surgical attempt. Retrospective studies involving patients in all 3 of these "designations" are significantly biased by patient selection and are difficult to interpret even when matched with historical or concomitantly treated "controls." What is generally apparent though, is that most patients do achieve some level of tumor reduction after chemotherapy, and surgery is facilitated with better odds of achieving an "optimal" status.

The answer as to whether the strategy makes a difference in a "hard point" such as survival is really the purview of randomized, prospective trials. Two have been completed and 1 published. Not surprisingly, the conclusions reached by these 2 trials are not uniform. In the trial reported by van der Burg et al, biopsy-proven ovarian cancer patients left with more than 1 cm residual disease following initial surgery were treated with 3 cycles of platinum-based chemotherapy before being randomized to either 3 more cycles of chemotherapy or to a second, interval cytoreduction attempt followed by 3 cycles of chemotherapy.[8]

This latter, experimental cohort demonstrated improved progression-free and overall survival compared to the conventionally treated suboptimally debulked patients. The benefit was significant and amounted to a gain of a median 5 and 6 months, respectively. In the second trial, conducted by the Gynecologic Oncology Group (GOG), all patients underwent a maximal effort at cytoreduction and were left with greater than 1 cm residual disease.[9] All patients received platinum and paclitaxel chemotherapy, but the experimental group underwent a second cytoreduction attempt after 3 cycles if their disease had not progressed (77% of randomization cohort). No difference was observed for either progression-free or overall survival between the interval debulking cohort and the conventionally treated cohort. Operative morbidity was acceptable and similar between cohorts for both trials. Numerous differences between the trials are noteworthy, but unaddressed is the estimation of inherent tumor biology, which may more strongly influence survival and is likely unaffected by "brawn." Currently, a trial by the EORTC is attempting to address this question by randomizing patients ahead of any surgical debulking to either a conventional approach or to neoadjuvant chemotherapy followed by surgery. This ambitious project will help provide a frame of reference to when and where aggressive surgery should be performed and how it will influence the natural history of ovarian cancer. One point is clear, however—patients who never undergo surgery, either because of medical infirmity or incomplete chemotherapy response, fair poorly. Limited options are available for this group. ■

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Adjuvant Vaccine for Renal Carcinoma: Finally!

ABSTRACT & COMMENTARY

Synopsis: *In this phase III, randomized, multicenter trial, renal carcinoma patients with organ-confined tumors were randomized after radical nephrectomy to receive autologous renal tumor cell vaccine or observation. The primary clinical outcome was the time to tumor recurrence. Patients who received the vaccine had greater 5-year and 70-month progression-free survival rates and lower tumor progression hazard rates than those in the control group.*

Source: Jocham D, et al. *Lancet*. 2004;363:594-599.

At present, 3% of all malignant tumors in adults develop in the kidney. Of these, 85% can be considered renal-cell carcinomas with the tumor originating from cells of the proximal tubules. After radical nephrectomy, organ-confined renal-cell carcinoma is associated with tumor progression in up to 50% of patients. Several adjuvant protocols, including radiotherapy, interferon alfa, interleukin 2, and medroxyprogesterone acetate, have been used in attempt to halt this progression. However, none have been effective in improving progression-free survival or overall survival in patients with renal-cell carcinoma.[1] Jocham and colleagues from the University of Lübeck Medical School in Germany examined the effect of an autologous renal tumor cell vaccine on the risk of tumor progression in

379 patients with stage pT2-3b pN0-3 M0 renal-cell carcinoma scheduled for radical nephrectomy. All patients were centrally randomized to receive autologous renal tumor cell vaccine (6 intradermal applications at 4-week intervals postoperatively) or no adjuvant therapy (control group). Patients were then assessed at 6-month intervals for a minimum of 4.5 years.

Overall, the patients who received the vaccine had better outcomes than those in the control group. In the vaccine group, 5-year and 70-month progression-free survival rates for patients at all tumor stages were 77.4% and 72%, respectively and 67.8% and 59.3%, respectively for the control group. At 5-year and 70-month follow-up, the hazard ratios for tumor progression were 1.58 (95% CI, 1.05-2.37) and 1.59 (1.07-2.36) respectively, in favor of the vaccine group (P = .0204, log-rank test). The vaccine was well tolerated, with only 12 adverse events among the 177 patients who received, in total, 1053 vaccine doses.

After subgroup analysis in which tumor size was among various features examined, Jocham et al conclude that autologous renal tumor cell vaccine is a beneficial approach, particularly for those undergoing radical nephrectomy due to organ-confined renal-cell carcinoma of more than 2.5 cm in diameter.

COMMENT BY WILLIAM B. ERSHLER, MD

The single greatest chance for long-term survival in patients with renal cell carcinoma is early detection and surgical excision before metastatic disease is apparent. The NCI SEER data indicate that 54% of renal carcinoma is localized at the time of diagnosis, and yet for these, nearly half will have recurrent disease. Various measures have been used, including chemotherapy, radiation and immunotherapy, in the adjuvant setting to diminish recurrences, but none have proven efficacious.[1]

The current study is remarkable for a number of reasons. First, it is a large study of a relatively uncommon tumor (renal carcinoma accounts for 3% of malignancies in adults)[2] and Jocham et al should be credited for a job well done with regard to community participation and patient recruitment. Secondly, the coordination of autologous vaccine preparation and administration for a relatively large number of individuals at multiple centers throughout the country must also have been logistically complex and may wrongly have been considered unfeasible by some at the outset. Again, Jocham et al should take credit for this outstanding effort. Finally, and most importantly, the findings are of great significance with regard to the role of vaccine therapy for this disease. For a tumor that characteristically is resistant to both chemotherapy and radiation, it is encouraging to demonstrate a beneficial response to immunotherapy, and with little toxicity.

There were some methodological concerns raised in an accompanying editorial,[3] such as a rather steep post-randomization attrition rate, particularly from the vaccine group, and the lack of data on overall survival.[3] However, these do not diminish the importance of the findings reported, but just raise a cautionary warning before we adopt a cumbersome and expensive approach as a clinical standard. With this trial as a starting point, additional studies should be designed to confirm the salutary effect in terms of overall survival and to identify which subsets of patients are likely to be protected. Furthermore, it would be of great value to determine the mechanisms of vaccine-induced protection and ultimately to develop more global vaccines that do not rely on the processing of autologous tumor tissues. ■

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Prophylactic Mastectomy and the Prevention of Breast Cancer in BRCA1/2 Carriers

ABSTRACT & COMMENTARY

Synopsis: *In a multi-institutional cooperative effort, Rebbeck and colleagues followed the course of 105 women with either BRCA1 or BRCA2 germline mutations who had elected bilateral mastectomy as a breast cancer preventive measure. Only 2 cases of breast cancer developed in this group of operated patients compared with 184 cases in the control group, demonstrating a remarkable risk reduction of > 90%. Although there are some methodological concerns with regard to the higher than expected incidence of breast cancer in the control group (even for those with BRCA mutation), the data clearly indicate a significant risk reduction and strengthen the rationale for prophylactic mastectomy in selected patients with germline BRCA mutations.*

Source: Rebbeck TR, et al. *J Clin Oncol*. 2004;22: 1055-1062.

Women with the germline BRCA1 or BRCA2 (BRCA1/2) mutations have a markedly increased risk of breast and ovarian cancer (73% risk to age 70). Some may elect bilateral prophylactic mastectomy in

order to reduce their risk of developing breast cancer. However, there are limited data on the efficacy of this approach. Rebbeck and colleagues from the PROSE Study Group followed 483 women with disease-associated germline BRCA 1/2 mutations. Of these, 105 had elected bilateral prophylactic mastectomy and 378 were matched controls (women with similar BRCA1/2 mutations who did not elect to undergo bilateral prophylactic mastectomy and were without known breast cancer). All women were followed for a mean of 6.4 years.

Of the 105 BRCA 1/2-mutation carriers with bilateral prophylactic mastectomy in the study, 2 (1.9%) were diagnosed with subcutaneous breast cancer post surgery, occurring 2.3 and 9.2 years later. Of the 378 controls (nonoperated), 184 (48.7%) developed breast cancer. Thus, compared with controls, the occurrence of breast cancer after bilateral prophylactic mastectomy corresponded to a hazard ratio of 0.05 to 0.09. These data demonstrate that bilateral prophylactic mastectomy significantly decreases the risk of breast cancer in women who carry these mutations. Bilateral prophylactic mastectomy reduces the risk of breast cancer by approximately 90%, translating into an overall breast cancer risk in BRCA1/2 mutation carriers of 7% to age 70. Additionally, in women with prior or concurrent bilateral prophylactic oophorectomy, bilateral prophylactic mastectomy reduced the risk of breast cancer by approximately 95%.

COMMENT BY WILLIAM B. ERSHLER, MD

Thus, bilateral prophylactic mastectomy reduces the risk of breast cancer in BRCA1/2 mutation carriers, as observed by the 90% risk reduction demonstrated in this series. After a mean follow-up of 5.5 years, only 2 cases developed among the 105 who underwent prophylactic mastectomy. Without question, this was significantly fewer than expected. Yet, the estimation of the actual risk reduction might have been overly inflated in this report by some difficult-to-control for methodological factors that were detailed in the accompanying editorial by Hartmann and colleagues.[1] Of the 378 matched controls, 184 (49%) developed breast cancer over a mean follow-up of 6.4 years. This is an unusually high incidence, even for mutation carriers, suggesting that one or more inherent biases in matched-control selection were of operational importance. Rebbeck and colleagues recognized these potential confounding factors and performed additional analyses by which the risk-reduction value of prophylactic mastectomy remained apparent.

Although we remain without a prospective, randomized trial, the data on the efficacy of prophylactic mastectomy has been strengthened by this report, and must be considered sound.[2-4] Nonetheless, the issues remain complex at all levels; biological, psychological, social and financial. For those who remain fundamentally opposed to this surgical approach, other methods of disease prevention need to be developed. In this regard, hormonal manipulations such as the use of anti-estrogens are under exploration, but success may be hampered by the known hormone receptor independence of the majority of breast cancers that develop in BRCA1 carriers.[5]

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Cervical Adenocarcinoma and Squamous Cell Carcinoma Incidence Trends Among White Women and Black Women in the United States

ABSTRACT & COMMENTARY

Synopsis: *Changes in screening, endocervical sampling, nomenclature, and improvements in treatment likely explain the increased in situ cervical SCC incidence in white women and black women. Increasing AIS incidence over the past 20 years in white women has not yet translated into a decrease in invasive AC incidence.*

Source: Wang S, et al. *Cancer*. 2004;100:1035-1044.

It is widely recognized that cervix cancer incidence rates have declined greatly in the United States following introduction of the Papanicolaou smear. However little is known about these rates among different histological subtypes. Wang and colleagues from the National Cancer Institute analyzed the Surveillance, Epidemiology, and End Results (SEER) database to evaluate this trend for a 25-year period, ending in the year 2000. The SEER Program

collects data from 9 geographically distinct population-based cancer registries and is available for public analysis. Incidence rates by histologic subtype, namely adenocarcinoma and squamous cell carcinoma, race, age and disease stage were computed and analyzed for trends. For both races, overall incidence of invasive squamous cell carcinoma declined over time and the majority of tumors currently detected are carcinoma *in situ* and localized cancers. Most striking was an increase in the incidence of squamous cell *in situ* disease reported over the final decade of analysis. Adenocarcinoma *in situ* rates among both races has increased and adenocarcinoma incidence has increased among young white women. In black women, invasive adenocarcinoma increases with age. Wang and colleagues conclude that changes in screening, endocervical sampling, nomenclature and improvements in treatment likely explain the increased squamous cell carcinoma *in situ* and decreased invasive squamous cell carcinoma incidence rates among both races. However, unlike this histology, the increased incidence of adenocarcinoma *in situ* diagnosis has not yet translated into a decreased incidence of invasive adenocarcinoma. The relationship of adenocarcinoma incidence and age among black women may reflect lack of effective screening or differential disease etiology.

COMMENT BY ROBERT L. COLEMAN, MD

One of the greatest successes in cancer prevention in the United States is undoubtedly the Pap smear. Introduced to a speculative audience by Dr. Papanicolaou in the 1940s, the Pap smear is now ubiquitously available, the focus of national screening programs (such as the National Breast and Cervical Cancer Early Detection Program) and individually responsible for a dramatic decrease in disease-specific mortality witnessed over the last 60 years. In many ways it is the ideal screening tool for a disease, which, by its nature, is screen-able. Yet nearly half of new cervical cancer cases occur in women either previously unscreened or infrequently screened.

In this study, Wang et al accessed the SEER Program to evaluate recent trends in the diagnosis of significant lesions (*in situ*, localized, regional and advanced) by histology (squamous cell vs adenocarcinoma), race (white and black), and age. This database represents about 10% of the US population and has been particularly useful in providing insight into population-based cancer trends. While inconsistencies in data reporting and lack of precise parity with individual cancer staging criteria are limiting, the large number of available patients allows analysis of otherwise inevaluable trends and rare diagnoses. In the current study, the strength of the database is used to evaluate cancer trends of the uncommon adenocarcinoma histology and its incidence among different races and ages. What is of particular interest is the relationship of *in situ* disease and cancer. It would seem logical that if our efforts in screening were successful, we should identify more pre-invasive conditions resulting in declining rates of cancer. This stage migration effect is clearly confirmed among both races for squamous lesions. Unfortunately, the same has not yet been realized for adenocarcinoma lesions, particularly among black women. In recent years, cytopathologists and investigators have not only become more savvy in making these diagnoses on Pap smears but also have modified the criteria of reporting these lesions so as to not confuse them with their squamous counterparts. However, many studies continue to report not only increasing adenocarcinoma to squamous cell carcinoma ratios but also real increases in new adenocarcinoma diagnoses. In the current study, adenocarcinoma incidence is increasing, particularly among young (25 to 34 years old) white women and in all age groups of black women. Interestingly, incidence rates of invasive adenocarcinoma plateau at about age 35 for white women yet continue to increase in blacks, being highest in the 75 and older cohort. If screening practices are equivalent, why is this effect being seen?

The answer is not immediately available in the current report. However, some hypotheses may be drawn in evaluating known risk factors for invasive adenocarcinoma and balancing these against population trends over the study time interval. Nulliparity and obesity have been associated with cervical adenocarcinoma risk and both have increased in recent years. Although a hormone effect from endogenous obesity may influence incidence, it has been hypothesized that just the occurrence of obesity may interfere with effective population-based screening and complicating detection. Still, the age-effect seen between the races suggests an etiological factor not heretofore identified. HPV-18 is most often HPV subtype associated invasive cervix adenocarcinoma. It is unknown if prevalence rates have altered over the last 25 years or whether the cofactors previously mentioned interact with this viral infection to effect this observation. More mechanistic investigation is needed.

In the big picture, significant progress is being made in the United States thanks to the tireless efforts of our healthcare providers. More needs to be done to ensure that all women are appropriately screened and managed for pre-invasive disease. However, the worldwide bur-

den problem cannot be overlooked and it is hoped an effective model can be enacted in those high-risk populations where resources are more limited. ■

Suggested Reading

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CME Questions

12. In the report by Rebbeck et al regarding prophylactic mastectomy for BRCA1/2 carriers, the reduction in risk of breast cancer development was estimated to be:

a. 5%.
b. 40%.
c. 90%.
d. 100%.

13. Of the current modalities available for the post-nephrectomy treatment of organ-confined renal cell carcinoma which has been clearly shown to produce significant enhancement of overall survival.

a. Chemotherapy
b. Radiation
c. Autologous vaccine
d. Allogeneic vaccine
e. None of the above

14. Which of the clinical features below is not considered predictive of clinical response to gefitinib (Iressa®)?

a. Adenocarcinoma with bronchiolar features
b. Female sex
c. Advanced age
d. History of never smoking

Answers: 12 (c); 13 (e); 14 (c)

In Future Issues: **The Role of Ketoconazole in the Treatment of Prostate Cancer**

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Risk of Adenocarcinoma in Barrett's Esophagus

Source: Murray L, et al.*BMJ(USA)*. 2003;3:534-535

ALTHOUGH SURVEILLANCE OF BARrett's esophagus (BES) for early detection of esophageal adenocarcinoma (E-CA) has become routine, the cost efficacy of this intervention is only scantily described.

Population data from Northern Ireland include all incident cancers. Murray and colleagues identified all subjects who had undergone esophageal biopsies with a diagnosis of BES between 1993 and 1999 and followed them up until 2000 identifying the number of subjects who were ultimately diagnosed with E-CA. Subjects who were diagnosed with E-CA within 6 months of the initial biopsy were not included in the data analysis.

Of 15,670 esophageal biopsies, almost 3000 met criteria for BES. In a follow-up period of 3.7 years (range, 1-8 years) 29 E-CA cases were identified. The mean yearly rate for E-CA was 0.26%, and 2.5 times higher in men than women. Risk was greatest in men older than 70 with specialized intestinal metaplasia found at esophageal biopsy, in whom the annual incidence was > 1%. Murray et al comment that when E-CA annual risk is 1%, surveillance may be cost-effective but that based upon these data, restricting surveillance to only the "high-risk" population would miss two-thirds of the incident cases of cancer. Our knowledge about the optimum schedule for BES surveillance remains incomplete. ■

Long-Term Effect of Doxazosin, Finasteride, and Combination for BPH

Source: McConnell JD, et al. *N Engl J Med*. 2003;349:2387-2398.

BENIGN PROSTATIC HYPERPLASIA (BPH) is commonly treated with alpha blockers such as doxazosin (DOX), alpha reductase inhibitors such as finasteride (FIN), or both. Long-term trials of DOX and FIN in combination have not been previously available to allow clinicians to compare the effect of alpha blockers, alpha reductase inhibitors, or both upon BPH symptoms. In addition to the value of symptom control, long-term treatments that reduce the need for surgical intervention are desired by clinicians and patients alike. Previous trials of alpha reductase inhibitors alone have indicated success in reducing the need for surgical intervention and the frequency of acute urinary retention.

Approximately 3000 men with symptomatic BPH who had not previously undergone surgical intervention, and whose PSA was < 10, were randomized to placebo, DOX, FIN, or DOX + FIN. The primary outcome was the first occurrence of a meaningful increase in the AUA symptom score (4 points or greater on a scale of 30).

Compared to placebo, both FIN and DOX had a statistically significant effect on the AUA symptom score (34-39% risk reduction). For this same end point, the benefit of combination therapy (DOX + FIN) was significantly greater than either agent alone. The risk of required surgical intervention or acute urinary retention was significantly reduced by FIN and DOX + FIN, but not DOX alone. Clinicians now have multiple logical options for long-term treatment of BPH. ■

Once Daily Valacyclovir to Reduce Herpes Transmission

Source: Corey L, et al. *N Engl J Med*. 2004;350(1):11-20.

AMONG GENITAL HERPES VIRUS (HSV-2) discordant couples, couples in whom one partner is HSV-2 infected and the other has not been, several strategies have been used to reduce likelihood of transmission to the uninfected partner. None of the strategies, save abstinence, can provide perfect assurance that HSV-2 transmission will not occur.

Asymptomatic persons shed HSV-2 and place their sexual partners at risk of transmission even during asymptomatic periods. It has been reported that subclinical viral shedding is the primary source of HSV-2 transmission. Antiviral treatment can reduce both the amount of time subclinical viral shedding occurs and the intensity with which virus is shed.

HSV-2 discordant monogamous couples (n = 743) were randomized to 500 mg valacyclovir QD (VAL) vs placebo for 8 months.

Only 4 of 743 susceptible partners on VAL developed symptomatic infection during the study period, compared with 16 placebo recipients (hazard ratio = 0.25). Similarly, seroconversion was found in 14 of 743 VAL-treated susceptibles, vs 27 of 741

on placebo. Placebo-treated patients excreted HSV-2 on 10.8% of days, compared with 2.9% of days with VAL treatment.

Once-daily VAL can reduce, but not eliminate, HSV-2 transmission. ■

Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea

Source: Mueller C, et al. *N Eng J Med*. 2004;350:647-654.

The etiology of acute dyspnea (DSP) can be diverse, and it is often especially difficult to separate pulmonary from cardiac causes. Recently, brain natriuretic peptide (BNP)—so called because of its original identification in porcine brain—has become recognized as a valuable diagnostic tool because it promptly rises in response to pathologic cardiac ventricular wall stress (eg, heart failure), and its levels are proportional to the degree of cardiac dysfunction. BNP is not affected by pulmonary conditions such as COPD, unless COPD has been of sufficient severity to result in right ventricular failure.

Whether standard clinical evaluation or BNP-based diagnosis provides more effective management for acute DSP was studied in this trial (n = 452) Primary end points were time to discharge and cost, both of which would be presumed to be adversely affected by inaccurate initial diagnosis.

Evaluation for all patients in the emergency department included an initial history and physical, EKG, oximetry, blood chemistry, chest X-ray and (for half of the group) point-of-contact BNP testing (15 minute on-site results). A BNP level > 100 pg/mL was considered sufficiently elevated to be consistent with heart failure.

Use of BNP testing provided an advantage for time-to-discharge from the ED (63 minutes vs 90 minutes), need for hospitalization (75% vs 85%), time to hospital discharge (8 days vs 11 days), and intensive care costs ($874 vs $1516)

Use of BNP testing, in concert with traditional diagnostic tools, shortens the time to initiation of specific and appropriate treatment, and hospitalizations. Overall, use of the BNP test reduced total treatment cost by more than 25%. ■

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Association Between C-reactive Protein and Age-related Macular Degeneration

Source: Seddon JM, et al. *JAMA*. 2004;291:704-710.

Age-related macular degeneration (AMD) is an important cause of loss of visual acuity, and because there are few effective treatments, enhanced prevention is paramount. The association between some cardiovascular risk factors (eg, smoking, dyslipidemia, obesity) and AMD has not gone unnoticed. Since C-reactive protein (CRP) has been associated with cardiovascular risk, it has become an item of interest whether CRP is similarly associated with AMD.

Study subjects (n = 4757) comprised persons with mild (n = 1063), intermediate (n = 1621), and advanced (n = 956) AMD, and controls (n = 1117). Subjects were followed every 6 months with tests of visual acuity and fundoscopy.

CRP levels were particularly discordant in persons with advanced AMD compared to those with no AMD. Even after statistical adjustment for age, sex, smoking, and obesity, CRP levels maintained a relationship with AMD. Persons in the 90th percentile for CRP had almost a 2-fold increased odds ratio for AMD. Seddon and colleagues suggest that CRP elevation is an independent risk factor for AMD. Since this is the first evidence to implicate inflammation (as manifest by CRP) etiologically in AMD, it remains to be shown whether modulation of CRP might have favorable effects on this end point. ■

VZV Reactivation in Astronauts

By Carol Kemper, MD, FACP

Source: Mehta SM, et al. *J Med Virol*. 2004;72:174-179.

Stress is a known trigger for reactivation of herpes viruses. Just the physical and psychological trauma of swapping alpha-male mice between 2 mouse colonies and the resultant battle for new alpha-male-dom has been shown to trigger reactivation of HSV in about half the mice. Herpes zoster can also reactivate after stress, including the stress of surgery.

After a 47-year-old healthy astronaut developed herpes zoster 2 days before a space flight, Mehta and associates decided to examine whether the stress of space flight can result in the reactivation of VZV. A total of 312 saliva samples, obtained from 8 astronauts before, during, and after space flight were examined by PCR. Amazingly, 61 of 200 (30%) specimens obtained during and after space flight were positive, compared with 1 of 112 (< 1%) obtained in a 234-265 day period before flying. No VZV was detected in 88 samples from 10 control subjects, who did not fly. Seven of 8 astronauts had at least 1 positive specimen during flight (2-12 days), while all 8 had anywhere from 1-8 positive specimens within 15 days of returning to earth. ■

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PHARMACOLOGY WATCH

Estrogen Found to Not Affect Heart Disease, Breast Cancer

The NIH has halted the estrogen-alone wing of the Women's Health Initiative (WHI) a year before its scheduled end. The 11,000 postmenopausal women who have had a hysterectomy and were enrolled in the estrogen-alone trial recently received a letter informing them of the preliminary results of the study and asking them to stop their study medication. After nearly 7 years of follow-up it appears that estrogen alone does not affect the rates of heart disease or breast cancer (either positively or negatively), both key findings of the estrogen/progesterone wing of the study, which was halted in July 2002. The researchers did find, however, that estrogen alone led to a slightly higher incidence of stroke (8 per 10,000), similar to the rate found in the estrogen/progesterone wing. Estrogen alone was also found, however, to decrease the risk of hip fracture. The NIH statement also says that older women (65 and older) showed a trend toward increase risk of probable dementia or mild cognitive impairment with estrogen-alone treatment. All of the women in the study were taking Wyeth & Co.'s conjugated estrogen product, Premarin. The full results of the trial will be published in a major peer-reviewed journal in the next 2 months. The NIH statement concurs with the guidance from the FDA, which states that hormone use should be limited to treatment of moderate-to-severe menopausal symptoms, vulvovaginal atrophy, and prevention of osteoporosis (as a second-line drug). The NIH statement is available on its web site at www.nih.gov/news.

Antibiotics Associated With Cancer Risk

Is antibiotics use associated with an increased risk of breast cancer in women? The question, which was first raised decades ago, has been the subject of much debate, but now a new study suggests that the answer may be yes. Researchers looked at data from more than 10,000 female members of the Group Health Cooperative in Washington state and identified 2266 women with invasive breast cancer and 7953 randomly selected controls without breast cancer. The variable evaluated was cumulative days of antibiotic use over the study period from January 1993 to June 2001. Increasing cumulative days of antibiotic use was associated with increased risk of breast cancer. The categories were 0 days, 1-50, 51-100, 101-500, 501-1000, and > 1001 days. The odds ratios (95% CI) for breast cancer were, respectively, 1.00 (reference), 1.45 (1.24-1.69), 1.53 (1.28-1.83), 1.68 (1.42-2.00), 2.14 (1.60-2.88), and 2.07 (1.48-2.89) ($P < .001$ for trend). Increased risk was seen in all antibiotic classes, including women taking tetracycline or macrolides for treatment of acne or rosacea. After adjusting for age, length of enrollment, and use of postmenopausal hormones, the death rate from breast cancer also increased with cumulative days of antibiotic use. The authors conclude that use of antibiotics was associated with an increased risk of incidence of breast cancer and death from breast cancer; however, it cannot be determined

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from the study whether antibiotic use is causally related or whether the indication for use of antibiotics was the primary factor (*JAMA*. 2004; 291:827-835). The link between antibiotics for breast cancer is plausible since antibiotics affect intestinal microflora, thus affecting phytochemical metabolism in the gut. Phytochemicals are thought to play an inhibitory role in the carcinogenesis pathway. Antibiotics also affect immune and inflammatory responses, which may lead to mammary carcinogenesis. An accompanying editorial reviews the possible mechanisms of the antibiotic/breast cancer connection and suggests that this study provides more questions and answers but that further research is needed. In the mean time, antibiotic use in women should be scrutinized, especially when other treatment options are available (*JAMA*. 2004;291:880-881).

Topiramate Effective Against Migraine

Topiramate is an effective agent for migraine prevention, according to a new double-blind study of 483 migraine patients. The drug, which is approved for prevention of seizures, was used in maximal doses of 50, 100, or 200 mg for 18 weeks in patients aged 12-65, who had at least a 6-month history of migraine and averaged 3-12 migraines per month. Mean monthly migraine frequency decreased significantly in the 100-mg ($P = .008$) and 200-mg ($P \leq .001$) doses, and the benefit was seen within the first month of therapy. Migraine days and use of rescue medication were also significantly reduced in the 100-mg and 200-mg groups. Adverse events included paresthesia, fatigue, and nausea (*JAMA*. 2004;291:965-973). Johnson & Johnson has already received conditional approval from the FDA for topiramate for the indication of migraine prevention pending additional safety information.

Statin Therapy For Heart Failure

Statin therapy has been found to be beneficial for a number of chronic illnesses; now add 2 more to the list. Statins have been found to benefit patients with advanced ischemic and non-ischemic heart failure. Researchers from UCLA reviewed the records of 551 patients with systolic heart failure with ejection fractions of 40% or less. After risk adjustment, statin use was associated with improved survival without the necessity of urgent transplantation in both non-ischemic and ischemic heart failure patients (91% vs 72% [$P < .001$] and 81% vs 63% [$P < .001$], at 1-year follow-up, respectively) (*J Am Coll Cardiol*. 2004;43:642-648). A new, large, randomized trial shows statins may also reduce the risk of stroke. As part of the Heart Protection Study in the United Kingdom, 3280 adults with cerebrovascular disease and an additional 17,256 patients with other occlusive arterial disease or diabetes were randomized to simvastatin 40 mg per day or placebo. Over the 5-year treatment period, there was a significant 25% proportional reduction in the rate of first stroke (4.3% simvastatin vs 5.7% placebo; $P < .0001$). The entire benefit was found in reduction in ischemic stroke. There was no difference found in the rate of hemorrhagic stroke, either increase or decrease. Simvastatin also reduced the number of TIAs ($P = .02$) and requirement for carotid endarterectomy or angioplasty ($P = .0003$). Among patients with pre-existing cerebrovascular disease, there is no apparent reduction in the stroke rate, but there was a highly significant 20% reduction in the rate of any vascular event ($P = .001$). Interestingly, benefit was seen in all levels of LDL, even in patients with LDL levels less than 116 mg/dL. The authors conclude that statin therapy reduces the risk of ischemic stroke by one-quarter to one-third in these at-risk patients (*Lancet*. 2004;363:757-767).

FDA Actions

The consumer watchdog group Public Citizen is calling for the FDA to ban AstraZeneca's new statin, rosuvastatin (Crestor), because of the risk of myositis and rhabdomyolysis. The drug, which was introduced to the American market in September, has been associated with 7 cases of rhabdomyolysis, 9 cases of renal failure, and 1 death. Myositis is a class affect of statins, especially the high-potency statins like Crestor. AstraZeneca states that the drug has been used in more than 1 million patients and that its benefits outweigh the risks. The FDA banned Bayer's cerivastatin (Baycol) in 2001 because of more than 100 deaths associated with the drug due to rhabdomyolysis.

Drug Approved to Target Angiogenesis

The FDA has approved the first monoclonal antibody that targets tumor angiogenesis. Genentech's bevacizumab (Avastin) is approved for the treatment of metastatic colorectal cancer. The drug works by binding vascular endothelia growth factor, thus inhibiting the formation of new blood vessels in tumors. In clinical trials the drug was found to extend survival time in patients with metastatic colorectal cancer by several months. ■