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INSIDE

Gefitinib as a Last Treatment Option for Non-Small Lung Cancer: Durable Disease Control in a Subset of Patients

ABSTRACT & COMMENTARY

Synopsis: *Gefitinib's single-agent activity in a group consisting of pretreated NSCLC patients is confirmed. Side-effects of gefitinib were mild. Prolonged survival was associated with good PS and less significantly with a never-smoking history, female gender and histology. Additional studies on mechanisms of tumor control and selection of target populations for this remarkable new drug are warranted.*

Source: Haringhuizen A, et al. *Ann Oncol*. 2004;15:786-792.

NON-SMALL LUNG CANCER (NSCLC) IS THE LEADING CAUSE OF cancer death worldwide and the majority of patients present with advanced, incurable disease. Combination chemotherapy regimens using cisplatin have provided a modest survival advantage but outcomes after disease program is very poor. Newer therapies are clearly needed. The epidermal growth factor receptor (EGFR) has been shown to be expressed in a variety of solid tumors including NSCLC. High EGFR expression levels have been associated with an unfavorable clinical outcome, making this a promising target for anticancer therapy. Gefitinib (Iressa™) is an orally available inhibitor of the tyrosine kinase domain of the EGFR. Partial responses in NSCLC patients have been documented. Two phase II trials of gefitinib have compared doses of 250 mg/d and 500 mg/d in patients previously treated for NSCLC have demonstrated single agent activity of 250 mg/d but less toxic than the higher dose. The present study reports a retrospective analysis of patients with pathologically proven NSCLC who were enrolled in an expanded access program at the Netherlands Cancer Institute to allow compassionate use of gefitinib.

COMMENT BY STUART M. LICHTMAN, MD

This paper presents data from the expanded access program from May 2001 to September 2002. One hundred patients were

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offered gefitinib as a last treatment after failure of previous chemotherapy or if no other treatment options were available. Brain metastases were an exclusion criterion, but patients with performance status > 2 and short life expectancy were allowed to enter the program. The drug was given at 250 mg/d. The drug was supplied for an indefinite period until disease progression, unacceptable toxicity, or death. Retrospective analyses were made for response, survival and toxicity. Ninety-two patients were evaluable. The median age was 58 years (range, 33-76). One third of the patients had a performance status of > 2 and 86% had stage IV disease and 62% had adenocarcinoma including 6 patients with bronchoalveolar-cell carcinoma (BAC). Eighty-five (92.5%) of the patients had received chemotherapy with 94% receiving a cisplatin combination and 31% received more than one regimen. In total, 1478 weeks were analyzed (median, 10.7; range, 0.4-75.3). The objective response rate was 8.7% and the duration of the response ranged from 1.2 to 15.8+ months. Thirty-four (37%) experienced stable disease (confirmed for > 4 weeks). Responses were documented in patients with adenocarcinoma only and were more frequent among never smokers and did not show any relation to gender, age, number of prior chemotherapy regimens, time since last chemotherapy, time since diagnosis or stage of disease. After a median followup of 8 months, the median survival was 4.9 months and 1-year survival was 29%. Multivariate regression modeling showed only that patients with PS 2-4 had a significantly worse prognosis, while there was a trend toward better survival for females, never smokers and patients with adenocarcinoma/BAC. Age and disease stage were not significantly associated with overall survival. Treatment toxicity was modest with common side effects being grade 1-2 skin rash and diarrhea in 34% and 22% of patients respectively. One asymptomatic patient developed interstitial pulmonary changes during the first 4 weeks of treatment unrelated to tumor progression or infection. Upon prolongation of gefitinib therapy the radiographic changes disappeared and an objective response was observed.

This study demonstrates that gefitinib has a clear palliative role in the therapy of patients with previously treated NSCLC. Its activity compares favorably with other salvage treatments and the one-year survival rate of 29% also is remarkable when compared to standard chemotherapy regimens.[1] The low toxicity observed in this previously treatment population makes a clear alternative to further chemotherapy. The one possible patient with interstitial lung disease and the lower incidence in larger databases (~1%) should lessen fears of this complication.[2] Palliative radiotherapy was administered with the patients continuing to receive gefitinib with excellent palliative benefit without added toxicity. The longest survival was among the small subgroup of patients with BAC and no responses were seen in squamous cell patients despite that EGFR receptor expression is strongest in this subtype. However, the analysis of the patients in this report demonstrated that the effect of histology on survival is less important than PS and also confirms that prolonged symptom and disease control is possible without response. Haringhuizen and colleagues conclude that efficacy cannot be determined by response status alone. Therefore gefitinib's single agent activity and mild toxicity are confirmed in a NSCLC population for whom no other treatment options existed. The disease stabilization and survival data observed compares favorable to salvage chemotherapy regimens with less toxicity.[3] ■

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Cancer Screening for Older Women: The Importance of Health Status

ABSTRACT & COMMENTARY

Synopsis: *Cancer screening for older women remains an area of active investigation. One current recommendation is to perform screening for individuals with a life expectancy of 5 years or more, as early detection of tumor in these individuals is more likely to have an impact on survival. In this cross-sectional population based study from California, it is apparent that screening is currently applied to older women without consideration of health status. Thus, for many, mammography and Pap smears are being obtained with little hope of benefit.*

Source: Walter LC, et al. *Ann Intern Med*. 2004;140: 681-688.

In general, the rates of screening mammography and Papanicolaou (Pap) smears decrease with advancing age. However, the benefit of these cancer-screening tests is better predicted by health status than age alone. It is improbable that older women whose life expectancy is less than 5 years would benefit from screening mammography and Pap smears.[1,2] Previous studies examining associations between health status and recent receipt of cancer screening tests have been inconsistent. As a result, it is currently unclear to what extent screening mammography and Pap smears are actually targeted to healthy older women who may plausibly benefit from these tests and are avoided in older women with limited life expectancies and for whom the potential harms (additional diagnostic tests, surgery, etc) may outweigh the benefits. To examine this question, Walter and colleagues from San Francisco Veterans Affairs Medical Center and University of California, San Francisco conducted a cross-sectional population-based study using data from the 2001 California Health Interview Survey (CHIS). In this survey, 4792 women 70 years of age or older were separated into 4 distinct categories based on health status and were analyzed for the receipt of screening mammography within the previous two years and a screening Pap smear within 3 years. Health Status was assessed by using the Medical Outcomes Study 12-item Short Form Physical Summary Scale.

Overall, 78% of women included in the study reported receiving screening mammography within 2 years of the survey and 77% reported a recent Pap smear. In general, screening rates decreased with advancing age. For those 70-74 years of age, 88% reported screening mammography and 86% reported a screening Pap smear. In comparison, for those 85 years of age or older, 61% reported screening mammography and 60% reported a screening Pap smear. However, within each age category, the percentage of women who were screened did not significantly decrease with worsening health status ($P >$ 0.1 for all comparisons). Women 75 to 79 years of age in the worst health status category were more likely to receive a screening mammogram than women 80-84 years of age in the healthiest PCS-12 quartile (82% vs 66%; $P = 0.002$), despite life expectancy. In addition, except for women 85 years or older, those with the worst PCS-12 quartile reported the same or more screening Pap smears than those women in the best PCS-12 quartile. Greater than 50% of women 80 years or older and in the worse health quartile reported recent screening mammography or Pap smears, corresponding to approximately 81,000 mammograms and 35,000 Pap smears when extrapolating these data to the California population. In contrast, an estimated 97,000 women 70 to 84 years of age in the best two health status quartiles had not recently received screening mammography (95% CI, 85,000-109, 000) and 58,000 had not received a recent Pap smear.

COMMENT BY WILLIAM B. ERSHLER, MD

The current report indicates that physicians are not determining candidates for screening based upon health status. The incidence of breast cancer increases with advancing age and accordingly, mammography is more likely to reveal previously unrecognized lesions in older women. However, the impact of early detection might be of little consequence to individuals of limited life expectancy because of other comorbidities. This is the foundation for the recommendation to limit screening to individuals with a life expectancy of five years or more. In the current survey, it was encouraging to see a relatively high rate of screening in older women. However, it appears that a good deal of the screening is inappropriately prescribed. Physicians and other health care providers who prescribe screening should take note. It is health status and life expectancy that are determinants of who among geriatric patients might benefit from screening. If estimated survival is 5 years or more, screening is appropriate.

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Lower-Dose Chemo for SCLC: Comparable Results in Low PS Patients

ABSTRACT & COMMENTARY

Synopsis: *In a phase II trial, the combination of low-dose carboplatin and paclitaxel was shown to be well tolerated by elderly and, or frail (ECOG performance status 2) patients with advanced small cell lung cancer. Response rates and survival were comparable to those published for other combinations.*

Source: Neubauer M, et al. *J Clin Oncol*. 2004;22: 1872-1877.

Extensive small-cell lung cancer (ESCLC) accounts for approximately 20-25% of all lung cancer diagnoses.[1] Between 50-75% of all patients with small-cell lung cancer (SCLC) have extensive disease. Despite significant improvements in diagnosis and therapy for the past 10 years, the prognosis for patients with ESCLC remains poor. Currently, the standard treatment for patients with ESCLC is combination chemotherapy with cisplatinum (or carboplatin) plus etoposide. However, previous studies have demonstrated high levels of toxicity with this treatment regimen, most notably in older patients or those who have a compromised performance status (PS). Since this is primarily a disease of older individuals, alternative combinations and dosing schemes need to be assessed. Neubauer and colleagues from the Kansas City Cancer Center examined 77 eligible patients with ESCLC (50.6% male, 9.4% white, 44.2% with a PS of 2, median age 74 years) between July 2000 and December 2001 with the goal of evaluating the effects of lower doses of carboplatin and paclitaxel (AUC = 2 and 80 mg/m^2, respectively) within a shorter treatment time frame (administered on days 1, 8, and 15 of each 4 week cycle, continuing for up to 6 cycles). They were specifically interested in a group of patients that were considered relatively frail either due to advanced age or a compromised performance status. Participating patients were analyzed for 1-year survival, response rate (RR), time to progression (TTP) and safety of weekly paclitaxel plus carboplatin.

Sixty six of the 77 participants were assessable for response. Of these, 25 responded to treatment (one complete response and 24 partial responses), leading to a response rate of 38%. The estimated 1-year survival rate was 30% and the median survival was 7.2 months (range, < 1 to 24.4 months). The median TTP was 3.5 months (range, < 1 to 21.2 months) and the estimated progression-free survival rate was 8%. Neutropenia and fatigue were the most common grades 3 and 4 toxicities, occurring in 22.1% and 8.6% of participants, respectively.

COMMENT BY WILLIAM B. ERSHLER, MD

The current trial offers a new treatment regimen for older or frailer patients with extended disease small cell lung cancer. The regimen offers a relatively simple schedule, easily manageable in a community oncology office and the toxicities, although present, were considered less than more aggressive regimens (eg, cisplatin and etoposide). Yet, 36 of the evaluable patients had dose reductions on at least one occasion.

One concern regarding weekly paclitaxel in older patients is the common practice of using dexamethasone in relatively high doses (20 mg prior to each injection). The consequences of this have yet to be evaluated with regard to the immune and metabolic effects over the treatment course. With reduced dose paclitaxel and in elderly patients who are more likely to be immunocompromised, it is possible that lower doses of steroid would be required to prevent the hypersensitivity for which it is prescribed.

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Adjuvant Radiation Determined for Intermediate Risk Endometrial Cancer! Or has it?

Special Report by Robert L. Coleman, MD

The strength of a clinician's recommendation for patient care is greatest in data generated through carefully conducted experimental studies. In many cases, this quality of data is generated from randomized clinical trials where a novel intervention is compared against some standard of care. When properly designed and conducted, positive or negative results will general-

ly provide convincing evidence to support a change in that standard or refute one, particularly if the outcomes are independently confirmed. The US Preventative Services Task Force recognized the confusion of interpreting clinical studies generated a rating system which categorizes both the quality of evidence into 1 of 3 levels and the strength of recommendation into 5 levels.[1] In general, the best quality data (Level 1) and strongest recommendations (Level A) are assigned to data generated through randomized, controlled trials. In the gynecologic cancer business, therapeutic intervention trials, for example, have methodically, albeit slowly, refined the care of affected women, in many cases to the improvement of survival or the reduction of toxicity. With the "muscle" of an international cooperative group research network and expanded collaboration, confirmatory trials have been increasingly contemporaneously launched or provided important data in a timely fashion to help solidify important issues in the care of our patients.

And so it is in the care of women with early, but intermediate risk, endometrial cancer. This disease site will account for approximately 40,320 new cases this year and be responsible for about 7090 cancer-related deaths.[2] Fortunately, many new cases of this disease are early stage, low grade and cured with surgery. However, an important and sizeable fraction of patients are diagnosed either at an older age, with some element of myometrial invasion, or with a higher grade or atypical histology that increases the risk for recurrence. These features we have known for many years and have been well documented through careful surgical staging studies reported more than 20 years ago.[3-6] In addition, 3 randomized controlled clinical trials involving more than 1600 patients and spanning almost 4 decades have been completed (*see Table 1*).[7-9] So it may come as somewhat a surprise that we still don't have a clear answer to the question, "What's the best treatment for women with intermediate risk uterine cancer?"

The latest and likely most anticipated results were recently published and represented the efforts of 40 member Gynecologic Oncology Group institutions and 8 years of accrual.[7] In this trial, "intermediate risk" was defined as any grade non-clear cell or papillary serous adenocarcinoma with any degree of myometrial invasion (FIGO Stage IB, IC), confined to the uterus (FIGO Stage IIA & B [occult]) with negative lymph nodes and cytology. The source for this broad entry criteria was historical and rooted in a prior GOG trial (GOG #33) where patients included in this cohort would have a risk for disease recurrence of 20 to 25% at 5 years with nearly all recurrences occurring within the first 2 years.[4] Surgical staging was required for entry and while adequacy was left to the discretion of the primary surgeon, it included hysterectomy, bilateral salpingo-oophorectomy and nodal sampling from key nodal basins unless enlarged nodes were identified. In the latter case, these were to be biopsied, but if negative, the patient could be enrolled. Eligible patients were randomized to either standard pelvic radiation after surgery or no additional treatment. The primary end point was a variable termed recurrence-free interval (RFI) which was defined as "the time from study entry to clinical, histologic or radiographic evidence of disease recurrence." This is different from the traditional progression-free interval (which was also evaluated in the trial) in that patients who died of intercurrent disease were censored in survival statistics. Ordinarily, these events would be captured as "events." Over the long accrual period, 448 patients were randomized, of which, 392 (88% of total) were included in the final analysis (202 to surgery alone, 190 to surgery + radiation). In regard to the primary endpoint, disease recurrence was reduced by 58% (hazard ratio [HR], 0.42; 90% confidence interval [CI], 0.25- 0.73; $P = 0.007$). At 2 years, the recurrence rate was 12% vs 3% in the adjuvant radiation cohort. In fact, the 2 women with vaginal recurrences randomized to radiation actually never received the therapy but are included in the intent-to-treat analysis. Most of this difference was in isolated local vaginal recurrences where the risk at 2 years was significantly reduced from 7.4% to 1.6%. So far, so good, right?

Well, yes and no. While a reduction in cancer recurrence is always a good thing, unfortunately, the reduction didn't translate into a survival benefit (HR, 0.86; 90% CI, 0.57-1.29). This is largely the result of effective salvage radiation in cases of local vault recurrence. Four-year survival estimates were 86% for surgery and 92% for surgery and radiation. And, as anticipated, intercurrent disease was a significant contributor to mortality with nearly one-half of the patients dying from causes not related to their primary cancer. In addition, the study grossly overestimated recurrence risks. It was determined that the current sample size could detect with 80% power a 58% decrease in recurrence and a 56% decrease in death with its initial recurrence estimates. However, recurrence was far less than anticipated. This prompted a post hoc creation of a high intermediate risk group (HIR) and a low intermediate risk group (LIR). Criteria used for this new determination are listed in Table 2. Under the new allocation, 132 patients (one-

Table 1

Comparison of the Randomized Trials of Adjuvant Radiotherapy in Stage I Endometrial Cancer

Trial	Patients & Eligibility	Surgery	Randomization	Age (mean)	Locoregional recurrence	Survival	Severe Complications
Norwegian 1968-1974	540 Stage I	TAH-BSO	Brachytherapy vs Brachytherapy and Pelvic RT	60	7% vs 2% at 5 yrs $P < 0.01$	89% vs 91% at 5 years; P = NS	N/A
PORTEC 1990-1997	714 IB Grade 2-3 IC Grade 1-2	TAH-BSO	NAT vs Pelvic RT	66	14% vs 4% at 5 years; $P < .001$	85% vs 81% at 5 years $P = 0.31$	3% GI at 5 years (actuarial)
GOG-99 1987-1995	392 Stage IB, IC Stage II	TAH-BSO, lympha-denectomy	NAT vs Pelvic RT	~61	12% vs 3% at 2 years $P < 0.01$	86% vs 92% at 4 years $P = 0.56$	8% GI at 2 years (occult)

TAH-BSO: Total Abdominal Hysterectomy Bilateral Salpingoophorectomy

GI: Gastrointestinal Toxicity (Grade 3/4)

NAT: No Additional Therapy

RT: Radiotherapy

Adapted from: Creutzberg C, et al. Gynecol Oncol. 2004;92:740-743.

third of total) were determined HIR (70: surgery alone, 62: surgery + radiation) and had a 2-year recurrence of 27%; 260 were LIR with a 2-year recurrence of 6%. Analysis of the primary end point, RFI, again demonstrated a significant reduction of recurrence (HR, 0.42; 90% CI, 0.21-0.83) for those treated adjuvantly with radiation, but only among the HIR cohort. However, even with this secondary cohort allocation, survival was not significantly different with radiation (HR, 0.73; 90% CI, 0.43-1.26), although the authors state the benefit is somewhat lower.

The purported benefits of radiation do come at a premium though. In this trial, the combination of surgical staging and postoperative pelvic radiation produced more frequent and higher-grade gastrointestinal toxicity with the only 2 treatment-related deaths occurring in the radiation arm from intestinal injury. In summary, radiation given in adjuvant-to-surgical staging produces lower isolated local recurrences, without a clear improvement in survival and with more toxicity compared to surgery alone in patients with early stage endometrial cancer.

The results seem cogent, so what's the confusion? Three critical elements continue to keep the controversy vibrant. First, surgical staging, while the mantra of contemporary care in the United States, is not universally accepted among investigators and, even among its advocates, comprises a range of procedural intents. Results from the large PORTEC trial concluded that adjuvant pelvic radiation produced a similar reduction in isolated vaginal recurrences among a slightly differently defined intermediate risk cohort compared with surgery alone.[8] Patients in this trial did not undergo any formal surgical staging and as such had approximately one-third the bowel complications as the GOG trial (*see Table 1*). These authors opined (in a subsequent editorial) that surgical staging added little more than toxicity and should be avoided in many patients with early endometrial cancer.[10] In their view, in the absence of surgical staging procedures, radiation was associated with a better therapeutic ratio and should be administered in all such patients. On the other hand, surgical staging when performed as a complete lymphadenectomy identifies with precision patients who are at risk for pelvic and distant recurrence, and as such, call into question the merits of pelvic radiation if the at-risk nodal tissues are resected. Indeed, several advocates of therapeutic lymphadenectomy have reported rare pelvic recurrences in these patients not treated with radiation.[11-13] As isolated local failures are frequently salvaged, these authors opine that surgical staging, if complete, can reduce toxicity and cost from radiation without affecting survival—as similarly presented in the GOG trial. Although there is no consensus on the issue of surgical staging between the two camps, trials are underway to evaluate whether radiation can be modified (PORTEC-II) and what information is gained by formal surgical staging in stage I endometrial cancer (MRC-ASTEC).[10]

The second element obstructing a consensus on the issue of adjuvant therapy is whether vaginal brachytherapy can be substituted for pelvic radiotherapy, regardless of whether surgical staging is done. In the only other randomized trial of clinically staged, intermediate-risk patients, loco-regional recurrences were significantly higher in women treated with adjuvant vaginal brachytherapy compared to adjuvant pelvic radiation and vaginal brachytherapy.[9] Survival, again, was not adversely impacted but staging data were not collected and presumably, some of these recurrences may have represented patients with occult stage IIIC disease. A comparative trial with carefully selected, but clinically defined intermediate-risk patients is underway in the Netherlands. A similar trial among formally staged patients has also been advocated.[14]

The third, and arguably most critical, element fueling the ongoing debate is the inconsistent definition of intermediate risk. As outlined above, the GOG intended to identify a risk cohort where recurrence would be expected in approximately 25% of accrued patients. However, by their definition, both a 45 year-old woman with 10% invasion of a grade I tumor and a 75 year-old woman with 95% invasion and cervical extension of a grade III tumor could have been equally enrolled. Clearly, these represent different risk groups. In the PORTEC trial, all stage IC grade III tumors were excluded, as were stage II patients. In some respects, while the recurrence rates and survival estimates are similar between these 2 recent trials, they represent different cohorts and lack sufficient power to evaluate important subgroups. The authors of the PORTEC trial have recently reported the outcomes of this latter excluded stage I cohort who were registered in the trial but were treated with pelvic radiation.[15] Ninety-nine of 104 such patients were followed for a median 83 months. In comparison to other randomized patients in the original trial, this patient cohort was characterized by significantly higher loco-regional relapse rates (14% vs 3%), shorter 5-year survival (58% vs 83%; HR, 5.5; $P < 0.0001$), and more frequent distant recurrence (32% vs 8%). Grade III was the most important prognostic factor to cancer-specific death by multivariate analysis. Effective therapeutic strategies in this cohort will need to address both loco-regional and distant failure. These data, thus, highlight the importance of case selection in constructing randomized protocols for intermediate-risk patients.

Fortunately, the quest for truth is embraced heartily in every generation. To this end, randomized trials of not only surgery but also radiation and chemotherapy are being planned and conducted in the worldwide gynecologic oncology theater. Eventually, these issues should be ironed out, but I for one am not sure if I should breathe a sigh of relief or hold my breath! ■

Table 2

Criteria For HIR Patient Allocation

Variable	Definition 1	Definition 2	Definition 3
Age (yrs)	≥ 70	≥ 50	Any age
Grade 2/3	Any 1	Any 2	Yes
LVSI*	Any 1	Any 2	Yes
Over 2/3 invasion†	Any 1	Any 2	Yes

* LVSI: Lympho-vascular Invasion

† Invasion is myometrial

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CME Questions

17. For advanced small cell carcinoma in elderly or frail (PS 2) patients, the combination of carboplatin (AUC = 2) and paclitaxel (80 mg/m^2) administered weekly for 3 weeks each month was found to be:

a. Less effective with regard to response rates and survival when compared to standard (cisplatin and etoposide) regimens.
b. More effective with regard to response rates and survival when compared to standard (cisplatin and etoposide) regimens.
c. Comparably effective with regard to response rates and survival when compared to standard (cis platin and etoposide) regimens but to be associated with less adverse events.
d. Comparably effective with regard to response rates and survival when compared to standard (cis platin and etoposide) regimens but to be associated with more adverse events.

18. In the report by Walter and colleagues regarding cancer screening in elderly women, which of the following conclusions may be drawn:

a. Young and elderly women are screened with equal frequency.
b. Elderly women with limited life expectancy due to comorbidities are screened with approximately the same frequency as healthy elderly women
c. Women above the age of 75 years are unlikely to receive benefit from screening.
d. Less than 40% of women beyond the age of 65 years are screened

Answers: 17 (c); 18 (b)

Readers are Invited. . .

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In Future Issues:

Laparoscopy for Primary Colorectal Cancer Resection

PHARMACOLOGY WATCH

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Missing Link Between Vaccines and Diabetes

A large cohort study from Denmark suggests no link between childhood vaccines and type 1 diabetes. The potential for such a link has been of concern for years because of the association between certain infections and the development of type 1 diabetes in children. Epidemiologists also noted that the incidence of type 1 diabetes has increased in developed countries along with a widespread use of vaccines in those countries. Danish researchers studied the records of children born in Denmark between 1990 and 2000, which represented 4,720,517 person-years of follow-up. In the cohort, 681 cases of type 1 diabetes occurred. The rate ratios for developing diabetes among children who received at least 1 vaccine compared to unvaccinated children were: 0.91 for *Haemophilus influenzae* type B vaccine, 1.02 for diphtheria/tetanus/polio vaccine, 0.96 for diphtheria/tetanus/pertussis/polio vaccine, 1.06 for whole cell pertus! sis, 1.14 for measles/mumps/rubella vaccine, and 1.08 for oral polio vaccine. No clusters of diabetes cases were found at any age level. The authors conclude that the data do not support the causal relationship between childhood vaccine and type 1 diabetes (*N Engl J Med*. 2004; 350:1398-1404).

Breast Cancer and the Use of Statins

Adding to the considerable evidence regarding the safety and efficacy of statins, it now appears that statins may slightly reduce the risk of breast cancer. Published in the "Early View" online journal *Cancer*, this case-control study was designed to assess whether statins were associated with an increased risk of breast cancer. At least 1 previous study has suggested an increased risk of breast cancer with statin use. The study looked at 975 women in Washington state who were diagnosed with primary invasive breast carcinoma, and were between 65 and 79 years old at the time of diagnoses. The comparison group was 1007 randomly selected women from the same residence area. Compared with non-users, current users, or ever-users of statins were not found to be at an increased risk for breast carcinoma. And in fact, the odds ratio of statin users was 0.9 compared to non-statin users (95% CI, 0.7-1.2). Long-term statin use of > 5 years was related to an even lower odds ratio of 0.7. The authors conclude that statins are not associated with an increase risk of breast carcinoma, and may in fact impart a reduced risk among long-term users (*Cancer* April 26, 2004).

Warnings Issued for IBS Drugs

Tegaserod (Zelnorm-Novartis), the heavily promoted serotonin 5-HT4 partial agonist for the treatment of irritable bowel syndrome (IBS), is the subject of new warnings by the FDA. The drug is indicated for women with IBS whose pri-

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mary symptom is constipation. The warning is the result of reports of diarrhea leading to hypovolemia, hypotension, and syncope in a small number of patients. There have also been rare cases of bowel ischemia in patients taking tegaserod, although no causal relationship has been found. Novartis has issued a "Dear Doctor" letter regarding the change in labeling dated April 26 (for more information see www.FDA.gov/medwatch). This is the second IBS drug to come under FDA scrutiny. The serotonin 5-HT3 antagonist alosetron (Lotronex-GlaxoSmithKline), for the treatment of IBS in women with severe diarrhea, was briefly withdrawn from the market in June 2002 because of over 80 cases of ischemic colitis associated with use of the drug. Alosetron became available again in December 2002 under a restricted use program.

What is the risk of a re-prescribing penicillin to penicillin allergic patient? The risk may be quite low according to a new study. Researchers looked at a database from the UK General Practice Research Database which included over 3.3 million patients who received penicillin. More than 6000 patients reported an allergy to the initial prescription, however, 48.5% of those patients were given the second prescription for penicillin at least 60 days later. Of those 3014 patients, only 57 (1.89%) had another event after the second prescription. This was much higher than the rate of reactions in patients who had not had an initial reaction (odds ratio, 11.2; [95% CI 8.6-14.6]), however, the absolute rate of reactions in patients who had an initial allergic reaction was quite small (*J Allergy Clin Immunol.*2004:113; 764-770). An accompanying editorial pointed out that even anaphylactic reaction had a low rate of recurrence with repeat exposure (1 out of 16) (*J Allergy Clin Immunol.*2004:113;605-606). And, while no one is recommending rechallenging patients with penicillin allergies, the low rate of repeat reactions is a far cry from the reported 60% rate of previous studies

FDA Actions

The FDA has removed the warning for lactic acidosis from metformin (Glucophage) and metformin extended release (Glucophage XR). Once considered the most serious side effect associated with metformin, a recent meta-analysis showed that there were no reports of lactic acidosis during more than 20,000 patient years use of the drug (*Arch Intern Med.*2003;163:2594-2602).

The FDA has approved apomorphine injection (Apokyn-Bertek) for hypomobility associated with Parkinson's disease. Hypomobility or "off periods" become more frequent with advanced Parkinson's disease and may occur at the end of a dosing interval or may occur spontaneously. A subcutaneous injection of apomorphine is effective for both types of “off periods.” However, because the drug causes severe nausea, it must be taken with an anti-emetic—although, not a 5HT3 antagonist because the combination may cause hypotension and syncope.

Aventis has received approval to market insulin glulisine (Apidra), a new rapid-acting insulin. The drug is a novel recombinant DNA human insulin analogue that is designed to be given 15 minutes before a meal or within 20 minutes after starting a meal. With a rapid onset and short duration of action, it is designed to cover mealtime blood sugar spikes. Aventis is marketing insulin glulisine to be used in combination with insulin glargine (Lantus), the company's long-acting basal insulin preparation.

The FDA has approved changes in prescribing information for finasteride (Proscar-Merck) that include concomitant use of the alpha-blocker doxazosin for the treatment of benign prostatic hyperplasia. Finasteride is a 5-alpha-reductase inhibitor. The combination was recently found to be better than either drug alone in reducing the overall clinical progression of benign prostatic hyperplasia (NEng J Med.2003;349:2387-2398).

Telithromycin (Ketek-Aventis) has been approved by the FDA for marketing for the treatment of community-acquired pneumonia including pneumonia caused by drug-resistant pneumococcus, sinusitis, and acute exacerbations of chronic bronchitis. Telithromycin represents the first of a new class of antibiotics known as ketolides. It is an oral tablet that is given once a day. ■