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INSIDE

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Promising Long-Term Results of Imatinib for CML

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD, MS

Section of Hematology Oncology, University of Chicago

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

Synopsis: *Imatinib inhibits the BCR/ABL tyrosine kinase in CML, leading to improved responses over standard therapy. This report provides 5 year follow-up from the seminal IRIS study of upfront imatinib for chronic phase CML among the 553 patients randomized to 400 mg of imatinib. The estimated best complete cytogenetic response was 69% and 87% at 12 and 18 months, respectively. Sixty-nine percent were still on imatinib after 5 years. Overall survival was 89% at 5 years with 7% progressing to accelerated-phase or blast crises. Grade 3 or 4 adverse events decreased with longer time on treatment. The majority of patients achieve durable remissions using imatinib as initial therapy for chronic phase CML.*

Source: Druker B, et al., for the IRIS Investigators. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. *N. Eng. J. Med.* 2006;355:2408-2417.

The translocation creating the Philadelphia chromosome results in the Bcr-Abl fusion protein and represents the central event in Chronic Myeloid Leukemia (CML). Imatinib (Gleevec™, originally known as STI-571) inhibits the aberrant tyrosine kinase activity of Bcr-Abl. It became quickly apparent that single agent imatinib had considerable activity in CML with low toxicity.[1] These exciting results quickly translated into a definitive randomized study of CML chronic phase, comparing imatinib to the standard therapy of interferon alfa and low dose cytarabine.[2] More than 1100 patients were enrolled in the Phase III International Randomized Study of Interferon and STI571 (IRIS). The estimated rates of complete cytogenetic response in the imatinib arm were 76% compared to only 14.5% with standard therapy. The long-term outcomes remained unclear in light of the relatively short follow-up of 19 months and a cross-over design. The

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study continued to monitor patients and thus now offers a more complete picture of the durability of responses and long-term imatinib tolerability.

The IRIS study enrolled 1106 subjects between 18 and 70 years of age with chronic phase CML within 6 months of diagnosis and not previously treated, except for hydroxyurea or anagrelide. Patients were randomized to imatinib at 400 mg daily or the combination of subcutaneous interferon alfa with low dose cytarabine. Cross-over to either arm was allowed because of poor responsiveness or toxicity. Patients were enrolled over a relatively short period of time between June 2000 and January 2001. The censor date for the analysis of January 31, 2006 allows 5 years follow-up for the last enrolled patient.

Only 3% (16/553) continued with their randomized arm of interferon alfa plus cytarabine while 69% (382/553) stayed with their initial assignment of imatinib. Thus, long-term results are reported only for the imatinib treated patients. The vast majority of the 382 imatinib treated patients were still taking 400 mg daily (82%). Grade 3 and 4 adverse events were very uncommon after year 2, primarily consisting of neutropenia (3%) and "other" drug related adverse events (4%).

The rate of major and complete cytogenetic responses for imatinib-treated patients was 89% and 82%, respectively. Among the 382 subjects still receiving imatinib at 5 years, 96% had a complete cytogenetic response. Only 6% (35/553) assigned to imatinib progressed to accelerated phase. Five percent lost a major cytogenetic response and 2% died from unrelated causes. The proportion on treatment who failed declined after year 2, from 7.5% in the second year, to 4.8%, 1.5%, and 0.9% in the third, fourth, and fifth year, respectively. Among the 350 patients who had a complete cytogenetic remission after 12 months of imatinib, 97% had not progressed, whereas 81% had not progressed among those not achieving a major cytogenetic response by 12 months of imatinib.

Five year overall survival was 89% (95% CI, 86 to 92) by intention to treat in the imatinib-assigned patients. Forty-four patients eventually underwent allogeneic transplant, of which 32% had died.

COMMENTARY

These updated results from the IRIS study summarize outcomes for newly diagnosed chronic phase CML using imatinib as front-line therapy. The 89% survival at 5 years is excellent and better than prior studies in the pre-imatinib era. The cross-over design prevents determination of a survival benefit compared to interferon alfa with cytarabine. Nevertheless, the low toxicity and persistent control of disease solidifies the recommendation of imatinib as initial therapy for chronic phase CML for most patients.

Reaffirming the positive results was the remarkable fact that among those who achieved a major cytogenetic remission at 12 months, only 3% developed disease progression at 5 years. Among those who achieved a cytogenetic remission, only a subset of 124 was tested for BCR-ABL transcript levels. Of those with a three-fold log BCR-ABL reduction, no patient progressed. Progression rates appeared to decrease with each year on therapy. The authors postulated that the decreasing rate of disease progression is consistent with the hypothesis that BCR-ABL mutations conferring resistance are primarily present at diagnosis, rather than evolving during therapy.

A major question remains whether we can identify newly diagnosed chronic phase CML patients for whom imatinib will not induce durable remissions. The present strategy has been to follow the kinetics of response during imatinib therapy either by cytogenetics or BCR/ABL transcripts and consider novel tyrosine kinase inhibitors and/or transplant in cases of inadequate responses. Mutational sequencing may also guide therapy. The Sokal score[3] helped predict responses with an 89% complete cytogenetic response rate for low-risk disease and 69% for high-risk patients. These differences may warrant closer monitoring of high-risk patients by Sokal score, but do not appear great enough to justify a different treatment strategy for patients having a high Sokal score.

Toxicity rates also decreased each year on therapy. A concern about serious cardiac toxicity was recently raised

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when a series of 10 cases were reported due to Imatinib.[4] However, in the IRIS study, only a single case was reported. Further post-marketing surveillance will be required to define the true incidence of this complication.

In summary, imatinib as initial therapy for chronic-phase CML shows excellent 5 year disease control and tolerability. ■

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Trastuzumab in The Adjuvant Treatment of Breast Cancer: New Evidence from The HERA Study

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Trastuzumab has previously been demonstrated to be active against HER2 positive breast cancer when used in the metastatic setting. In a large multicenter clinical trial (HERA) in which trastuzumab was used after chemotherapy in an adjuvant setting, after a median two years follow-up, a significant benefit was observed for treated patients compared to the observational group treated with chemotherapy alone. A survival advantage in this setting demonstrable at only two years is a notable finding and is indicative of the importance of this agent in the treatment of HER2 positive breast cancer.*

Source: Smith I, et al. *Lancet.* 2007;369:29-36.

The gene for HER2, a transmembrane growth factor, has been shown to be amplified in 15-25% of women with early breast cancer and is considered a marker of aggressive disease.[1,2] Trastuzumab (Herceptin®), a humanized monoclonal antibody against the extracellular domain of the HER2 receptor, has been shown to provide overall survival benefit to women with HER2-positive metastatic breast cancer either administered alone[3,4] or in combination with chemotherapy.[5,6] The Herceptin Adjuvant (HERA) trial is one of several large trials conducted by the Breast International Group (0101) designed to test the efficacy of trastuzumab in the adjuvant setting for women with HER2-positive disease. Results for a first planned interim analysis with a median 1 year follow-up showed that trastuzumab given every 3 weeks for 1 year after adjuvant (or neo-adjuvant) chemotherapy achieved a significant improvement in disease-free survival compared with women treated with adjuvant chemotherapy alone.[7] Several other trials have reported similar results.[8,9] The current report is an analysis of the HERA trial in terms of overall survival at a median follow-up of two years.

The HERA trial is an international intergroup open-label phase III randomized trial involving women with centrally-confirmed HER2 positive early stage invasive breast cancer who had completed local regional therapy and a minimum of four courses of predefined standard adjuvant (or neoadjuvant) chemotherapy. Eligibility criteria included node-positive disease (or node negative if the pathological tumor size was larger than 1 cm). Patients with locally advanced disease were excluded. Enrolled patients were randomized to receive trastuzumab at an initial dose of 8 mg/kg and maintenance dose of 6 mg/kg every 3 weeks for either 2 years (n = 1701 patients) or 1 year (n = 1703 patients. A third group received no trastuzumab. Patients enrolled on the two-year trastuzumab arm continue on therapy and are not included in this report.

Disease-free survival is the primary endpoint of the HERA trial and overall survival a secondary endpoint. Analysis of the overall survival data at two years, however, indicates a small, but significant improvement. There were 59 deaths in the trastuzumab group compared with 90 in the control group. The unadjusted hazard ratio (HR) for the risk of death with trastuzumab compared with observation alone was 0.66 (95% confidence interval 0.47-0.91; p = 0.0115). Furthermore, there were 218 disease-related events (distant, CNS, locoregional, contralateral breast, second malignancy) with trastuzumab compared with 321 in the control group, and the unadjusted HR for the risk of an event with trastuzumab compared with observation alone was 0.64 (0.54-0.76; p < 0.0001).

COMMENTARY

It has become quite apparent that trastuzumab is an effective treatment for metastatic breast cancer. Now, data from the HERA study lends additional evidence for its use in the adjuvant setting. The demonstration that one year of treatment with trastuzumab following adjuvant chemotherapy is of benefit in terms of both disease-free[7] and overall survival, and the latter being demonstrable after only two years of follow-up is a testament to the advisability of this approach. Of all the adjuvant chemo/hormonal treatments for breast cancer, only Tamoxifen revealed a survival advantage as early as two years.[10]

There remain two critical issues with regard to trastuzumab use in the adjuvant setting. The first relates to whether it should be used concurrently with chemotherapy, as typically prescribed in the US, or sequentially as in the HERA trial. It is conceivable that the delay of several months (average 8.5 months in the HERA trial) could influence the overall efficacy in a negative way. In fact, preliminary analysis of NCCTG N9831 presented at ASCO 2005 suggested concurrent (ie, trastuzumab with chemotherapy) may be more effective than sequential treatment (Perez, et al.), but a more complete analysis from this important trial remains forthcoming.

The second question concerns the duration of trastuzumab treatment. As mentioned, the third arm of the HERA trial includes women treated for two years rather than one. Yet, it may turn out that even shorter treatment duration is equally efficacious. In this context it is notable that in a relatively small trial (232 patients) a significant disease-free survival benefit was observed after only 9 weeks of trastuzumab treatment given concurrently with chemotherapy in the adjuvant setting.[9]

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Having Sons Reduces The Risk of Prostrate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a family-based research cohort, men were followed for up to 40 years after the birth of their children, and those with only daughters had a 40% higher risk of prostate cancer compared with men with at least one son. The findings support the hypothesis that Y chromosome loci are involved in the pathogenesis of prostate cancer.*

Source: Harlap S, Platiel O, Friedlander Y, Calderon-Margalit R, Deutsch L, Kleinhaus KR, Manor O, Neuget AI, Opler M, Perrin MC, Terry MB, Tiram E, Yanetz R. Prostate cancer in fathers with fewer male offspring: The Jerusalem Perinatal Study Cohort. *J Natl Cancer Inst.* 2007;99:77-81.

There have been recent studies suggesting the involvement of loci on the Y chromosome in the pathogenesis of prostate cancer. Because mutations or variants in sex chromosomes might influence the gender of offspring, the current study was designed to determine whether the risk of prostate cancer is associated with offspring gender. For example, mutations on the Y chromosome associated with prostate cancer (as postulated) may also reduce the likelihood of male offspring.

To address this question, investigators surveyed vital status and cancer incidence in fathers from the Jerusalem Perinatal Study, a family-based research cohort.[1] Over a 13-year period (1964-1976), all births to residents in western Jerusalem (n = 92,408) were recorded and demographic features of parents and grandparents abstracted. By linking with the Israel Cancer Registry it was discovered that a total of 712 of the fathers had developed prostate cancer.

Compared with men who had at least one son, men with only daughters had an increased risk of prostate cancer (adjusted relative risk [RR] = 1.40, 95% confidence interval [CI] = 1.20 to 1.64, P < 0.0001). In men with one, two, or three or more offspring, the relative risks associated with absence of sons were 1.25 (95% CI = 1.00 to 1.56), 1.41 (95% CI = 1.04 to 1.91), and 1.6 (CI I.05 to 2.43), respectively. Men with no daughters showed no statistically significant altered risk, compared with men who had offspring of both sexes. The relative risk of prostate cancer decreased as the numbers of sons increased (Ptrend < 0.0001) but did not change with the number of daughters.

COMMENTARY

These findings support the hypothesis that Y chromosome loci are involved in prostate cancer and provide an excellent example of how careful epidemiological investigation can provide basic clues to the pathogenesis of disease. Of course, other explanations may be forwarded. One that came to mind was that perhaps men with daughters are more likely to be screened and thus diagnosed. However, if such were the case, earlier diagnosis would be expected in those with daughters and better survival observed. This was not the case. Furthermore, the lack of sons appeared to have biological significance, as it becomes increasingly important as family size increases.

Although the postulated genetic loci on the Y chromosome remain to be identified, further research capitalizing on this observation may be productive. Prior work had suggested involvement of sex chromosomes, both X.[2, 3] and Y. The incidence of prostate cancer is increased in some[4, 5] families carrying mutations in BRCA1 or BRCA2. In such families, regardless of whether they include men with prostate cancer, male carriers have a lower percentage of male offspring than the general population.[6, 7] This was also found in two case-control studies of the offspring of BRCA-associated prostate cancer patients.[8, 9] Thus, the Jerusalem Perinatal Study provides additional evidence that function of the Y chromosome is altered in some ways in at least some with prostate cancer. Further investigation in the laboratory, but using clinical samples, may ultimately reveal the specifics of this Y chromosome defect. ■

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Decline in Breast Cancer and Reduced Use of Hormone Therapy

ABSTRACT & COMMENTARY

By Leon Speroff, MD

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Dr. Speroff is a consultant for Barr Laboratories and does research for Wyeth

Synopsis: *Breast cancer statistics indicate a rapid decrease in prevalence immediately after the publicity surrounding the reports from the Women's Health Initiative.*

Source: Ravdin PM, et al. A sharp decrease in breast cancer incidence in the United States in 2003. San Antonio Breast Cancer Symposium, December 14, 2006.

Ravdin and colleagues from the University of Texas M.D. Anderson Cancer Center reported a 7% decrease (14,000 fewer cases) in the incidence of breast cancer in 9 regions of the U.S. in 2003.[1] This decrease occurred in women over age 50 and consisted of two to three times as many estrogen receptor positive tumors. The steepest decline was observed in women ages 50-69. Clarke and colleagues from California reported the breast cancer incidence for the years 2003 and 2004 in the Northern California Kaiser program and for the 13-county Kaiser catchment area.[2] Coincident with the post-Women's Health Initiative decline in postmenopausal hormone use, the breast cancer incidence declined 10% in Kaiser members and 11% in the area's population.

COMMENTARY

These reports highlight the currently most important unanswered question: Does postmenopausal hormone therapy cause an increase in breast cancer or do the epidemiologic data reflect an impact of hormone therapy on pre-existing tumors? The most striking feature of these recent reports is the short latent period between discontinuation of hormone therapy and a reduction in prevalence. This is consistent with the uniform findings in case-control and cohort studies of an increase in breast cancer risk only in current users, with a rapid reduction after cessation of treatment. The current reports are consistent with breast cancer statistics derived from the area around Geneva, Switzerland, indicating the other side of the coin. Beginning in 1997, the peak of breast cancer incidence in the Geneva area increased in a younger group of women (ages 60-64), and the increase occurred only in Stage I and Stage II disease with estrogen receptor positive tumors in hormone users.[3]

These effects of hormone therapy are in keeping with the multiple reports of better outcomes in hormone users diagnosed with breast cancer because of better-differentiated tumors,[4, 5] an effect that can be interpreted as a beneficial consequence. Another finding that is consistent with an effect on pre-existing tumors is the fact that not a single study thus far has reported a risk increase for non-invasive disease. If hormone therapy were initiating (causing) new tumor formation, one would expect to see an increase in in-situ disease.

Even the M.D. Anderson Cancer Center authors pointed out that their data most likely primarily reflect existing cancers just below the detection limit in 2002 that slow or stop their growing. Thus, a serious question is raised: What will the statistical data show in the coming years? Will some of the pre-existing tumors be overcome by body defenses and disappear? Will tumors that emerge later be of later stage and grade disease with poorer outcomes? At this point in time, we must recognize that hormone therapy could be having a favorable effect on breast cancers. ■

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Defining Prognostic Features in Triple-Negative Breast Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Breast cancers that are "triple-negative" (ie, ER, PR, HER2-negative) are considered high risk, yet there remains variability, with some demonstrating less malignant features than others. In an effort to further define this group, UK investigators performed additional laboratory assessments and correlated these with outcomes in a series of patients from their institution. In addition to established clinical parameters (tumor size, nodal status, etc.), of the additional tests, androgen receptor and cytokeratin basal phenotype were shown to offer the most useful prognostic value.*

Source: Rakha EA, et al. Prognostic markers in triple-negative breast cancer. *Cancer.* 2007;109:25-32.

Breast cancers that are devoid of estrogen and progesterone receptors are more likely to be poorly differentiated, of higher histological grade, associated with a higher recurrence rate and decreased overall survival.[1, 2] Nonetheless, there are certainly examples of hormone receptor beast cancers for which these aggressive features are not observed.[3, 4] The absence of the HER-2 receptor is considered favorable because HER-2 positive tumors have a higher growth fraction and are associated with a higher recurrence rate and decreased overall survival.[5] Yet, HER2 negative cancers are also very heterogeneous with regard to clinical course.

Rakha and colleagues from Nottingham, UK report an evaluation of a well-characterized series of

breast cancer patients with particular attention to those with the "triple-negative" phenotype (ie, estrogen receptor-negative, progesterone receptor-negative, and HER2-negative). Their goal was to determine how best to stratify subsets and characterize proliferative potential based upon available microarray and immunohistochemical panels. Of the 1944 cases of invasive breast cancers observed at the Nottingham Tenovus Primary Breast Carcinoma Series between 1986 and 1998, 16.3% were of the triple-negative phenotype. The median OS survival for the whole series was 73 months and time of event-free survival was 66 months. The triple-negative phenotype was associated with larger size, higher grade, more frequent distant metastasis and an overall poorer prognosis. Additional studies performed on these samples included an assessment of expression of androgen receptor, epidermal growth factor receptor (EGFR), P-cadherin, E-cadherin, basal cytokeratin (CK5/6, CK14) and p53. Within the group of triple-negative tumors, nodal status, tumor size, and the presence of androgen receptor provided the greatest prognostic value. Additionally, associations were found with loss of expression of E-cadherin and gain in expression of basal cytokeratins (basal phenotype), P-cadherin, p53 and EGFR. Of the 282 triple negative cases, 178 were LN negative and 104 were LN positive. In the LN positive group, size and androgen receptor expression had significant prognostic value. In the LN negative group, however, only the basal phenotype (cytokeratin expression), which was associated with a more negative outcome, demonstrated prognostic value. The authors concluded that for those patients found to have "triple negative" breast cancer, further assessment to determine androgen receptor expression (favorable) and cytokeratin "basal phenotype" should be undertaken to refine prognosis and develop treatment strategy.

COMMENTARY

Breast cancer is typically classified by tumor size, histological features, nodal status, hormone receptor status and the presence or absence of distant metastases. Under most circumstances this is sufficient information to formulate rational treatment strategies. Yet, there remains variability in outcome, and this presumably in some way is related to the variability in malignant properties of the cancer cell. This, coupled with the availability of new technology allowing a more detailed classification of gene expression, opens the possibility for developing an even more precise classification system; one that would more accurately predict tumor aggressiveness and response to therapy.[6, 7] The current report is a step in that direction. Within the 'triple-negative' breast cancer phenotype there is variability with regard to clinical outcome. Much of this can be predicted by clinical parameters (nodal status, tumor size, etc.), but it appears that for those that express androgen receptor, clinical course might be expected to be somewhat more favorable. In contrast, expression of the basal cytokeratin phenotype would be considered unfavorable, particularly within the lymph-node negative group, a finding consistent with other studies.[8, 9]

Hopefully, these findings and others yet to come will not only provide prognostic information, but direction with regard to specific, targeted therapies. ■

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CME Questions

5. **In this study of the 5 year outcomes in the IRIS study, what did the authors demonstrate about imatinib (gleevec) therapy for newly diagnosed chronic phase CML?**
   a. Best complete cytogenetic response rate of 87% at 18 months
   b. Very few patients could tolerate long-term imatinib
   c. Less than 50% were alive at 5 years
   d. Most patients eventually required an allogeneic transplant

6. **Data from the HERA study indicates benefit from trastuzumab for patients with early stage HER2 positive breast cancer in terms of:**
   a. disease free survival at one year follow-up
   b. disease free survival at two years follow-up
   c. overall survival at two years follow-up
   d. all of above
   e. none of above

7. **Based upon the Jerusalem Perinatal Study cohort, the risk for prostate cancer would be greatest in a man with:**
   a. three daughters, one son
   b. two daughters, two sons
   c. no daughters, one son
   d. two daughters, no sons.

8. **Of the following features, which offer prognostic value for the subset of "triple-negative" breast cancer patients:**
   a. Androgen receptor
   b. P-cadherin
   c. E-cadherin
   d. p53
   e. All of above

Answers: 5 (a); 6 (d); 7 (d); 8 (e)

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This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

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clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■