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Second Malignancy after Treatment of Hodgkin's Disease: The Influence of Treatment, Age, and Follow-up Time

ABSTRACT & COMMENTARY

Source: Abrahamsen A, et al. *Ann Oncol*. 2002;13:1786-1791.

Synopsis: Combination chemotherapy and extensive radiotherapy introduced in the late 1960s greatly improved survival rates in Hodgkin's disease (HD), but increased risk of second cancer was recognized from the early 1970s.[1] An increased incidence of acute nonlymphocytic leukemia (ANLL) in patients treated with chemotherapy alone or combined radiation therapy and chemotherapy, and solid tumors in those treated with radiation therapy or combined radiation therapy and chemotherapy, have consistently been reported. The development of secondary non-Hodgkin's lymphoma (NHL) has been reported following both radiation therapy and chemotherapy, which it has been claimed is not necessarily treatment related, but may be part of the natural history of HD. Increased risk of ANLL and NHL has been found up to 10 years after treatment. In contrast, second cancers increase steadily with time up to 20 years after treatment. It is not clear whether the increased risk of second cancers observed in the 10-20 years follow-up interval will continue to increase further with more prolonged follow-up, or level off or decrease at some point of time after > 20 years follow-up. In a recent study, HD patients treated during adolescence or young adulthood still had an increased risk of second cancer even > 20 years after first treatment.[2-4]

In this study, a follow-up of an adult patient population up to 30 years after initial treatment was presented. In the period 1968 to 1985, an unselected population of 1024 patients started treatment for HD at the Norwegian Radium Hospital and were followed for second cancer from 1969 through 1998 by the Norwegian Cancer Registry. The median age at diagnosis of HD was 40 years, and the median time at follow-up was 14 years.

There were 197 second cancers. Fourteen were ANLL, 31 NHL, and 152 solid tumors. The standardized incidence ratio

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(SIR) was significantly increased for second cancers as a group, and for the subgroups ANLL, NHL, lung cancer, breast cancer, stomach cancer, and melanoma. ANLL was related to heavy treatment with chemotherapy and combined chemotherapy and radiotherapy, NHL was not treatment related as there was an equal distribution among all treatment modalities, and solid tumors were related to radiotherapy only or combined modality therapy. The SIR of ANLL and NHL reached a peak between 5 and 10 years after treatment. Solid and nonsolid tumors increased with young age at diagnosis of HD and solid tumors increased with follow-up time up to 28 years. Their conclusion was that in this long-term follow-up study of HD patients of all ages, the SIR of solid tumors was high in patients treated at young age and decreased with increasing age at the time of treatment. Most solid tumors had started within or at the edge of the irradiated field, and SIR of solid tumors increased even 20-30 years after diagnosis.

COMMENT BY STUART M. LICHTMAN, MD, FACP

In addition there have been 2 recent papers addressing the same issue. Delwail and colleagues address the risk of secondary leukemia in patients treated by MOPP (mechlorethamine, vincristine, prednisone, procarbazine) or ABVD (adriamycin, bleomycin, vinblastine, DTIC) chemotherapy.[5] Between 1972 and 1988, 869 adult patients received MOPP (mechlorethamine, vincristine, procarbazine and prednisone; 462 patients) or ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine; 373 patients) and subsequent high-dose irradiation for HD. Nine patients developed a leukemia after MOPP and 4 after ABVD; 11 patients were diagnosed as ANLL and 2 as acute lymphoblastic leukemia (ALL). Both cases of ALL were observed after ABVD and were associated with an 11q23 translocation. The 15-year actuarial risk of secondary leukemia was 2.4% for the whole group of patients, 3.4% after MOPP, and 1.3% after ABVD. For the MOPP subgroup, the risk of leukemia was significantly associated with the extent of irradiation: 2.4% for limited irradiation and 13.9% for extended irradiation ($P < 0.001$). For the ABVD subgroup, this risk remained low (1.3%) whatever the type of irradiation. Concerning ANLL, the MOPP regimen was significantly associated with a higher risk: 3.4% vs 0.7% for ABVD ($P < 0.05$). The 15-year risk of ALL was 0.6 after ABVD regimen. This study demonstrated that ABVD induced less ANLL than MOPP. However, a low risk of ALL with an 11q23 translocation related to topoisomerase II inhibitors was observed.

Ng and associates analyzed 1319 patients with clinical stage I-IV Hodgkin disease.[6] Of these, 181 second malignancies and 18 third malignancies were observed. With a median follow-up of 12 years, the relative risk (RR) and absolute excess risk of second malignancy were 4.6 and 89.3/10,000 person-years. The RR was significantly higher with combined chemotherapy and radiation therapy than with radiation therapy alone. The risk increased with increasing radiation field size in patients who received combined modality therapy, and with time after HD. After 15 and 20 years, there was a 2.3% and 4.0% excess risk of second malignancy per person per year. The 5-year survival after development of a second malignancy was 38.1%, with the worst prognosis seen after acute leukemia and lung cancer. The excess risk of second malignancy after HD continues to be increased after 15-20 years, and there does not appear to be a plateau.

These 3 studies confirmed the excess risk of second malignancies in patients with HD. This is true for both solid tumors and hematologic malignancies. The risk seems to be extremely long and may never diminish throughout the patients' life. It is clear that while our first priority is the cure of HD treatment planning must

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take into account the potential for the development of secondary malignancy. All of these studies suggest that the risks may be reduced with smaller radiation field sizes and abbreviated chemotherapy. The need for combined modality therapy should be carefully considered in light of these studies. ■

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Beta-2-Microglobulin: Prognostic Indicator in Early Stage Hodgkin's Disease

ABSTRACT & COMMENTARY

Synopsis: Of 217 consecutive Hodgkin's disease patients seen at M.D. Anderson with Stage I or II disease who received chemo- and radiation therapy, 12 had elevated b2M (> 2.5 mg/L). There was a trend for reduced relapse-free survival for those with elevated levels, and a significant correlation with reduced overall survival. Thus, an inexpensive and widely available laboratory measure might provide useful prognostic information in patients with Hodgkin's disease.

Source: Chronos GM, et al. *Cancer*. 2002;95: 2534-2538.

Over an 8-year period (1987-1995) 217 consecutive patients with Stage I or II Hodgkin's disease (HD) were treated at M.D. Anderson Cancer Center in Houston with initial chemotherapy and radiation. Patients received a median of 3 cycles of combination chemotherapy followed by radiation. In the current report, various clinical features were examined to determine if they were of prognostic significance. Medical records were reviewed including beta-2-microglobulin (β2M), albumin, gender, and presence of bulky disease and relapse-free survival (RFS) and overall survival (OS) were recorded.

Patients were followed from 0.9 to 13.4 years (median, 6.6 years) and 92% were observed for 3 or more years. All patients were free of HD at the end of treatment. Twenty-eight patients developed recurrence and of these, 19 have died. The 5-year RFS and OS were 88% and 95%, respectively. A serum level of β2M > 2.5 mg/L was considered elevated and this level or higher was found in 12 of the patients.

With regard to RFS, male gender and bulky disease were statistically significant adverse prognostic factors ($P < 0.05$) on both univariate and multivariate analysis. There was a trend toward elevation of the serum β2M level also representing an adverse prognostic factor. However, with regard to OS, only β2M was a significant adverse prognostic factor on univariate and multivariate analyses.

■ COMMENT BY WILLIAM B. ERSHLER, MD

β2M is a single chain polypeptide of unknown function linked to the major histocompatibility complex Class I cell surface antigen.[1] Its presence in serum reflects lymphoid cell turnover, and elevated levels have been associated with a number of malignancies including multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and HD. In fact, β2M levels have been shown to correlate with stage in HD, and elevated levels have correlated with less favorable prognosis.[2-4] The current study adds strength to this correlation, inasmuch as the follow-up period was of sufficient duration that an association of elevated β2M with overall survival could be determined. However, it should be remembered that this was a retrospective analysis of a subset of HD patients (early stage disease, treated at a single institution), and only 12 patients had high β2M levels.

These caveats notwithstanding, a simple, widely available and inexpensive laboratory test may be of great value as a predictor of unfavorable outcomes, and thus may be useful in identifying those patients for whom more aggressive therapy is warranted. However, it would be premature to hinge clinical decisions on the β2M level. Such would be the recommendation only after the current findings are confirmed in a larger, multi-institutional analysis. Even then, β2M is likely to be just one of several prognostic factors, along with age, gender, presence of bulky disease, leukocytosis and lymphocytopenia, that may ultimately guide clinicians to the appropriate treatments for early stage HD. ■

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Follow-up Survival after Early Stage Laparoscopy in Women with Endometrial Cancer

ABSTRACT & COMMENTARY

Synopsis: Although longer follow-up is needed, the survival of women with early stage endometrial cancer does not appear to be worsened by laparoscopy.

Source: Eltabbakh GH. *Cancer*. 2002;95:1894-1901.

Eltabbakh retrospectively reviewed women presenting with clinical stage I endometrial cancer (according to the 1988 FIGO staging) at the University of Vermont. Women treated with laparoscopic surgery were compared with those treated with laparotomy with regard to their characteristics, surgical procedure, treatment, surgical stage, histology, tumor grade, and recurrence-free and overall survival. Factors affecting survival (surgical approach, histology, grade, and surgical stage) were evaluated using multivariate analysis. One hundred women underwent laparoscopy, and 86 underwent laparotomy from January 1996 through June 2001. Both groups were similar with regard to age, parity, menopausal status, lymphadenectomy, surgical stage, tumor grade, histology, and postoperative radiation therapy. Women who underwent laparoscopy and those who underwent laparotomy had similar 2-year and 5-year estimated recurrence-free survival rates (93% vs 94% and 90% vs 92%, respectively), as well as similar 2-year and 5-year overall survival rates (98% vs 96% and 92% vs 92%, respectively). There was no apparent difference with regard to the sites of recurrence between both groups. In univariate and multivariate analyses, surgical stage, tumor grade, and histology (but not the surgical approach) were found to have a significant effect on survival. Eltabbakh concluded that, although longer follow-up is needed, the survival of women with early-stage endometrial cancer does not appear to be worsened by laparoscopy. As one would expect, surgical stage, tumor histology, and tumor grade were found to significantly affect survival regardless of the surgical approach used.

■ COMMENT BY DAVID M. GERSHENSON, MD

Surgery remains the cornerstone of treatment for endometrial cancer. With the innovations in optics and equipment associated with laparoscopy over the past decade or so, new surgical approaches using LAVH + BSO and surgical staging have been explored by several groups worldwide. Since the early 1990s, several of these groups, including Dr. Eltabbakh's, have reported their experience in patients with early-stage endometrial cancer. A summary of the literature to date suggests that, compared with laparotomy, laparoscopic surgery for endometrial cancer is feasible, is associated with shorter length of hospital stays and less time off work, is associated with equivalent complication rates, and is associated with an enhanced quality of life. Furthermore, these groups have demonstrated that comprehensive surgical staging with bilateral pelvic lymphadenectomy and paraaortic lymphadenectomy is also feasible and results in resection of an equivalent number of lymph nodes compared with laparotomy. Some reports have also documented that laparoscopic surgery for endometrial cancer is safe in obese patients and in elderly patients. Based on encouraging information arising from these early reports, the Gynecologic Oncology Group (GOG) initiated a large randomized trial (Lap 2) comparing laparoscopic surgery with traditional laparotomy in women with early-stage endometrial cancer. Although this study is accruing patients at a very high rate, it will likely be a few years before we have mature data regarding sites of recurrence and overall survival. Other small studies have demonstrated equivalent survival rates in patients undergoing laparoscopic surgery vs laparotomy for endometrial cancer. To my knowledge, this is the largest study reported to date. However, the median duration of follow-up among women in the laparoscopy group was only 27 months—too brief to make a determination. In addition, the study is retrospective and likely does not include a large enough number of patients to demonstrate a difference in survival. It should be noted that there have not been any port site recurrences in the present study thus far. The findings of this study are of great interest, but only with the completion of the GOG's Lap 2 will the survival issue be definitively answered. ■

Dr. Gershenson is Professor and Chairman, Department of Gynecology, M.D. Anderson Cancer Center, Houston, Tex.

Cyclin E and Survival in Patients with Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: The hazard ratio for death from breast cancer for patients with high total cyclin E levels as compared with those with low total cyclin E levels was 13.3 to about 8 times as high as the hazard ratios associated with other independent clinical and pathological risk factors, including axillary node status.

Source: Keyomarsi K. *N Engl J Med.* 2002;347: 1566-1575.

Keyomarsi and colleagues introduce their article by noting that the prognosis for patients with newly diagnosed breast cancer is determined primarily by the presence or absence of metastases in draining axillary lymph nodes. However, about one third of women with breast cancer who are node negative suffer a recurrence, and about one third of those with positive nodes are free of disease at 10 years after local-regional therapy. The lack of predictability about survival derived from clinical disease stage and hormone receptor status drives the search for better prognostic markers of breast cancer survival. In this study, Keyomarsi et al examined the correlation between survival and tumor markers in 395 women with breast cancer followed for a median of 6.4 years. The molecular markers were cyclin E, cyclin D1, cyclin D3, and the HER-2/neu oncogene. Keyomarsi et al looked at levels of protein expression using Western blot analysis and traditional immunohistochemical techniques.

Cyclins are proteins that regulate cell growth. They are known as mitogens because high levels cause cell growth. Tumors often make aberrant versions of known proteins, and such is also true for breast cancer cells and cyclin E. In breast cancer cell lines, cyclin E is amplified, and the cyclin E protein is often constitutively overexpressed. Some of these cell lines overexpress not only the full-length version, but also up to 5 low-molecular-weight isoforms. In this study, Keyomarsi et al used a variety of assay methods to determine the levels of cyclin E and other molecular markers. Clinical data were obtained from tumor registries. Of the 114 patients with stage I disease, 12 had a recurrence of breast cancer and died of it with a median time to death of 4.1 years. All 12—and only those 12 of the 114 patients—had a high level of cyclin E. High levels of total cyclin E and high levels of low-molecular-weight cyclin E as assessed by Western blotting (but not by immunohistochemistry) were associated with hazard ratios for death from breast cancer of 33.0 and 20.8, respectively. In the article, Table 2 shows the factors that independently predict death from breast cancer. Those factors and their respective hazard ratios (with confidence intervals) are: positive nodes 1.8 (1.2-2.8); stage IIIB-IV 1.7 (1.1-2.5); negative estrogen-receptor status 1.8 (1.3-2.7); high level of low-molecular weight cyclin E 2.1 (1.1-4.0); and high total cyclin E 13.3 (5.8-30.2). Keyomarsi et al conclude that identifying those patients with poor prognosis breast cancer may spare some from the toxic systemic therapies now routinely administered.

COMMENT BY SARAH L. BERGA, MD

The reason to know about this study is that high levels of cyclin E, as assessed by Western blotting, were associated with a much larger hazard ratio for death from breast cancer than any other known predictor. In the accompanying editorial, Sutherland and Musgrove point out that cyclin E may induce chromosomal instability, a hallmark of cells that metastasize and respond poorly to chemotherapies, be they endocrine or cytotoxic.[1] As they note, it is metastases, not the rate of proliferation of the primary tumor, which causes death from breast cancer. Keyomarsi et al, in the source article, indicate the potential to identify patients who can be spared from aggressive intervention. It would also be wonderful to know if cyclin E correlates with past HRT use or whether "normal levels" can be used to identify patients likely to benefit from subsequent use of HRT. As the study of O'Meara so poignantly demonstrated, breast cancer survivors who used HRT lived longer and had fewer recurrences.[2] Perhaps the patients who lived long enough to take HRT belonged to the group already destined to survive by virtue of the breast tumor's biology, including, perhaps, low levels of cyclin E. In short, many of the questions with which we struggle, such as whether HRT causes breast cancer, make no sense unless breast cancer as an entity behaves homogenously. The present study makes evident that, indeed, not all breast cancers are the same. The corollary, then, is that we should not treat the primary breast cancers and the patients who have them as "the same." It is true that these findings are not ready for prime time because the assay methods are not widely available, but the lesson holds nonethe-

less. We must continue to find ways to appropriately individualize therapies, while eschewing simplistic assumptions about sameness and behavioral homogeneity. ■

Dr. Berga is Professor and Director, Division of Reproductive Endocrinology and Infertility,University of Pittsburgh.

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Outcomes of Endometrial Cancer Patients Undergoing Surgery With Gynecologic Oncology Involvement

ABSTRACT & COMMENTARY

Synopsis: Involvement of a gynecologic oncologist at the time of primary surgery for endometrial cancer was associated with comparable outcomes in both the university and community hospital setting.

Source: Pearl ML, et al. *Obstet Gynecol*. 2002;100: 724-729.

Pearl and associates undertook this study to compare the outcomes of patients with endometrial cancer who had primary surgery with gynecologic oncology involvement at university or community hospitals. The patients were divided into 2 groups based on whether their surgery was performed at a university or community hospital. There were no significant differences between the 2 groups with regard to Quetelet index; intervals between biopsy and consultation, consultation and surgery, and biopsy and surgery; estimated blood loss; incidence of operative or hospital complications; frequency of appropriate surgical staging; stage distribution; histology or grade; and hospital stay. Patients at a university hospital were significantly older, had a higher severity index, and were more likely to have had a vaginal hysterectomy and participate in a research protocol. Both the Quetelet index and the severity index were significantly higher for patients who had vaginal hysterectomy than for those who had either laparoscopically assisted vaginal hysterectomy or total abdominal hysterectomy. When analyzed by surgical approach, the frequencies of pelvic and para-aortic lymph node sampling were comparable between the groups. Both the Quetelet and severity indices were significantly higher for patients who did not have lymph node sampling. Pearl and colleagues conclude that involvement of a gynecologic oncologist at the time of primary surgery for endometrial cancer was associated with comparable outcomes in both the university and community hospital setting.

■ COMMENT BY DAVID M. GERSHENSON, MD

In recent commentaries on endometrial cancer, I have raised some issues related to adequacy of surgical staging comparing generalists with gynecologic oncologists. Because most general obstetrician gynecologists are not trained to perform lymph node sampling, they typically take one of 3 approaches: 1) involve a gynecologic oncologist; 2) involve another type of surgeon—general surgeon, urologist, etc; or 3) do not perform lymph node sampling. This article is focused on yet another important question: Do endometrial cancer patients have comparable outcomes, regardless of the setting—community-based vs university-based institutions? The simple answer is yes, in this case. One university-based gynecologic oncology group, operating in 2 university hospitals and 5 community hospitals, was able to deliver the same quality of care in these 2 distinct settings. Not surprisingly, university-based patients were older and had a significantly higher preoperative severity index, reflecting the fact that elderly and sicker patients are referred to a university setting more frequently. Of course, these were the same gynecologic oncologists operating in both settings. We don't really know how far we can extrapolate these findings; for instance, would similar findings be achieved if one compared a university-based group with a community-based group? Although I would predict that the answer is yes, we don't know this from the present study. In addition, I would underscore one other point not emphasized by Pearl et al: community-based patients were enrolled in clinical trials significantly less frequently than university-based patients—10% vs 26% (P = .004). We need to develop the infrastructures to make clinical trials more accessible to community-based patients. The pediatric oncology community has been very successful in this area, but the same is not true for adult cancer patients and their physicians. ■

Alcohol and Hormone Therapy Increase the Risk of Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: The Nurses' Health Study reports an increased incidence of breast cancer with daily alcohol consumption, hormone therapy, and an additive effect with greater drinking.

Source: Chen WY, et al. *Ann Intern Med*. 2002;137: 798-804.

Chen and colleagues from the nurses' health Study examined the self-reported questionnaire data from their prospective cohort. Comparing the results to nondrinkers and nonusers of hormone therapy, key results were as follows:

	Hormone Users	Adjusted Relative Risks For Invasive Breast Cancer
No alcoholic intake	< 5 yrs current use	1.45 (1.13-1.86)
	> 5 yrs current use	1.31 (1.05-1.66)
1.5-2.0 drinks daily	< 5 yrs current use	2.08 (1.41-3.08)
	> 5 yrs current use	1.99 (1.41-2.79)

An average intake of less than 1 drink daily did not increase the risk of breast cancer. Analyses including carcinomas in situ were similar. Past users of hormone therapy did not demonstrate an increased risk. Risks were similar comparing estrogen alone with users of combined estrogen and progestin, but the numbers of combination users were small.

■ COMMENT BY LEON SPEROFF, MD

The increase in risk for breast cancer associated with postmenopausal hormone therapy in this report from the Nurses' Health Study is essentially the same as that previously reported. The new observation in their cohort of nurses is that drinking 1.5-2 drinks of alcohol per day further increases the risk. Speculation about a possible mechanism focuses on the well-known demonstration that alcohol acutely increases the blood levels of estrogen.

A limitation of the study is that nurses who consumed 1.5-2 drinks daily amounted to about 10% at the beginning of the study in 1982 and decreased to about 7% a decade later. Nevertheless, the conclusions are consistent with other reports in the literature, and they are consistent with the proposed biologic mechanism.

These results do not differ from that recently published by the Women's Health Initiative. The magnitude of the breast cancer risk is in the same ballpark, and there remains the unanswered question whether the results reflect the effect of hormone therapy on pre-existing tumors. However, the magnitude of the relative risks in the Nurses' Health Study (as well as their reliability) can be questioned because of possible important differences comparing hormone users and nonusers. Based on previous Nurses' Health Study publications, the user group differs in several categories that affect the risk of breast cancer. Current hormone users in the study are more likely to have a history of benign breast disease, to be nulliparous, and to have given birth only once or twice. The Nurses' Health Study investigators have never adequately addressed this potential confounding of their results.

If the Nurses' Health Study conclusions are correct, the additive effects of hormone therapy and alcohol are a finding that differs with the Women's Health Initiative. According to the Women's Health Initiative, hormone therapy did not further increase the risk of breast cancer associated with other risk factors. However, the actual data were not provided and it is not entirely clear that the relationship between alcohol consumption and hormone therapy was adequately examined.

Basically, this report should change our interaction with patients only by further increasing our concern for women who drink alcohol daily and consume more than 1 drink daily. ■

Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland, Ore.

CME Questions

1. **Which of the following statements about serum b-2-Microglobulin in patients with Hodgkin's disease is true?**
   a. It is commonly found to be elevated, even in individuals with limited stage disease.
   b. Low levels are associated with earlier relapses in patients with advanced stage disease.
   c. Elevated levels at diagnosis, although infrequently observed, are associated with shorter survival in patients with limited disease.
   d. Elevated levels at diagnosis, although infrequently observed, are associated with higher relapse rates but not diminished overall survival in patients with limited disease.

2. **The following statements are true regarding the associations between alcohol and hormone therapy with the risk of breast cancer *except*:**
   a. One beer or one glass of wine, even if consumed daily, is not associated with an increased risk of breast cancer.

b. The breast cancer results in this new report from the Nurses' Health Study are in agreement with their previous reports.
c. The Nurses' Health Study is a randomized clinical trial.
d. According to the Nurses' Health Study, alcohol consumption and postmenopausal hormone therapy are independent risk factors for breast cancer.

3. Which of the following best predicts death from breast cancer?
a. Tumor stage
b. Axillary node status
c. Cyclin E
d. HER-2/neu oncogene
e. Estrogen receptor status

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In Future Issues:

Gemcitabine Activity in Nasopharyngeal Carcinoma

PHARMACOLOGY WATCH

FDA Approves Claritin For OTC Use For Seasonal Rhinitis

After years of legal wrangling, the FDA has approved loratadine (Claritin, Schering-Plough) as an over-the-counter (OTC) product for the treatment of seasonal rhinitis. Loratadine is considered a nonsedating antihistamine, and its OTC approval was linked with the FDA's work with the National Transportation Safety Board to improve public awareness about the concerns of drowsiness while driving associated with older antihistamines. The OTC switch also comes within months of loss of patent protection for loratadine and the entry into the market of generic equivalents. The OTC switch applies to all 5 formulations of Claritin, and at least 1 generic house plans to market "Reditabs." Meanwhile, Schering-Plough continues to aggressively market desloratadine, the active metabolite of loratadine under the trade name Clarinex, in an attempt to protect its $3 billion Claritin market.

Simpler Atrial Fibrillation Management

Management of atrial fibrillation (AF) may be simpler in the future based on the results of 2 studies published in the December 5, 2002, *N Engl J Med*. The larger of the 2 studies (AFFIRM) enrolled more than 4000 patients in the United States and Canada with AF and at least 1 other risk factor for stroke such as hypertension, coronary artery disease, diabetes, congestive heart failure, or age older than 65. Patients were randomized to a rhythm control strategy with cardioversion followed by amiodarone, sotalol, propafenone, or older antiarrhythmics such as procainamide or quinidine; or a rate control strategy with digoxin, beta-blockers, and/or calcium channel antagonists. All patients in both groups were anticoagulated with warfarin. The primary end point was overall mortality. The 5-year death rate was 23.8% in the rhythm control group and 21.3% in the rate control group (P = 0.08). Rhythm control was associated with more hospitalizations and more adverse drug effects. In the second study from The Netherlands, 522 patients with persistent AF after electrical cardioversion were randomized to treatment aimed at rate control or rhythm control. Both groups received oral anticoagulation, and the composite end point was death from cardiovascular causes as well as bleeding, implantation of a pacemaker, or severe adverse effects of drugs. After a mean duration of nearly 2.5 years, the primary end point occurred in 44 patients in the rate control group (17.2%) and 60 patients in the rhythm control group (22.6%) (P = 0.11). Although both studies showed trends toward adverse outcomes with rhythm control, neither study reached statistical significance. The authors of both studies suggest that a rate control strategy for the treatment of AF is at least as good as the rhythm control strategy. In an accompanying editorial, Michael D. Cain, MD, states that "on the basis of these data, rate control can now be considered a primary approach to the treatment of atrial fibrillation." He also suggests that nonpharmacologic treatments for AF will still be pursued with the goal toward maintaining

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sinus rhythm (*N Engl J Med*. 2002;347:1825-1833; 1834-1840; 1883-1884).

Oral Anticoagulation Vs Aspirin in AF

In a related study, oral anticoagulation was found to be superior to aspirin in preventing stroke in patients with atrial fibrillation (AF) or paroxysmal AF. The study was a pooled analysis of 6 trials of more than 4000 patients who were randomized to receive therapeutic doses of oral anticoagulant or aspirin with or without low-dose oral anticoagulants. Patients receiving oral anticoagulation were significantly less likely to experience stroke (2.4 vs 4.5 events per 100 patient years; hazard ratio [HR], 0.55), ischemic stroke (HR, 0.48), or cardiovascular events (HR, 0.71) but were more likely to experience major bleeding (2.2 vs 1.3 events per 100 patient years; HR, 1.71). Anticoagulant therapy also showed benefit on all-cause mortality but only after 3 years of therapy. Interestingly, more benefit was seen for anticoagulation vs aspirin in patients younger than 75 compared to those 75 years or older. A lesser benefit was also seen for women compared to men. The authors suggest that oral anticoagulation is more effective than aspirin in decreasing the risk of stroke and other cardiovascular events in patients with nonvalvular AF (*JAMA*. 2002;288:2441-2448).

Immunization Does Not Cause Autism

A new study should put an end to concern regarding the MMR (measles, mumps, and rubella) vaccine and its possible link to autism. Researchers in Denmark looked at the records of all children born between January 1991 and December 1998, representing a cohort of almost 540,000 children. Of those, 82% (440,655) received the MMR vaccine. In the cohort, 316 children were diagnosed with autism and 422 were diagnosed with other artistic spectrum disorders. After adjustment for potential confounders, the relative risk for artistic disorder in the vaccinated children compared to the unvaccinated was 0.92 (95% CI, 0.68 to 1.24). The relative risk for other artistic spectrum disorders was 0.83 (95% CI, 0.65 to 1.24). The authors also looked for a possible association between age at the time of vaccination, the time since vaccination or the date of vaccination, and development of artistic disorder and found no relationship. They also found no temporal clustering of cases of autism at any time after immunization (*N Engl J Med*. 2002;347:1477-1482).

Statins May Lower CRP Levels

C-reactive protein (CRP), an inflammatory marker, has shown to be a strong predictor of cardiovascular events, perhaps even more predictive then LDL cholesterol levels (*N Engl J Med*. 2002; 347:1557-1565). Most physicians have looked at these studies with interest but have been unsure what to do with an elevated CRP level in an individual patient. Perhaps even more importantly, it is unclear whether lowering CRP affects cardiovascular outcomes. Until an answer is found to this important question, an increasing body of evidence is suggesting that statins may lower CRP levels.

Simvastatin Reduced CRP Plasma Levels

A recent study reviewed the use of simvastatin in 130 patients with mixed hyperlipidemia and 195 patients with hypertriglyceridemia in a placebo-controlled, double-blind trial. After 6 weeks of treatment with simvastatin 20, 40, and 80 mg, significant reductions in CRP plasma levels were noted vs placebo ($P < 0.05$) (*Am J Cardiol*. 2002;90:942-946). CRP lowering by statins appears to be a class effect with multiple reports of benefit with various statins in the last 2 years.

FDA Actions

Roche's pegelated interferon alfa-2a (Pegasys) has been approved for use in combination with a ribavirin for the treatment of hepatitis C. The drug was approved in October 2002, but Roche has been eagerly awaiting the approval for combination treatment in order to compete with Schering-Plough's Peg-Intron/ribavirin combination for the same indication.

Eli Lilly has received approval to market atomoxetine (Strattera) for the treatment of attention deficit hyperactivity disorder (ADHD). Unlike other drugs for this indication, atomoxetine is not a stimulant and is not listed as a controlled substance. Rather, the drug is a selective norepinephrine reuptake inhibitor, which seems to play a role in regulating attention, impulsivity, and activity levels. Strattera is approved for treatment of ADHD in children, adolescents, and adults.

Eli Lilly has also received approval to market teriparatide injection (Forteo) for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture. Teriparatide is a portion of human parathyroid hormone, which stimulates new bone formation in the spine and hip. The drug is given by daily injection in the thigh or abdomen. ■