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## ABSTRACT & COMMENTARY

# Breast Cancer Risk Reduction for BRCA 1/2 Carriers by Bilateral Mastectomy

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Dr. Yates reports no financial relationships relevant to this field of study.

SYNOPSIS: In a prospective analysis, healthy women known to be carriers of BRCA1 or BRCA2 mutations chose either bilateral mastectomy or active surveillance. Ascribing to careful methodological detail, the investigators found that those who chose surgery had lower risk for breast cancer occurrence and better survival. Nonetheless, the authors note that longer follow-up and a larger sample size are needed to confirm statistical significance of their observations.

SOURCE: Heemskerk-Gerritsen BA, et al. Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: A prospective analysis. *Ann Oncol* 2013;24:2029-2035.

Germ-line BRCA1 or BRCA2 mutations carry an increased risk for the development of breast and/or ovarian cancer.[1,2] Strategies to reduce breast cancer risk include rigorous adherence to mammography or MRI schedules, chemoprevention, and bilateral risk-reducing mastectomy (BRRM). In addition, risk-reducing salpingo-oophorectomy (RRSO) aimed at reduction of ovarian cancer risk also reduces the risk of breast cancer.[3] Previous reports have described a reduction of breast cancer risk after BRRM in healthy BRCA1 or BRCA2 mutation carriers.[4-6] However, trials were small, retrospective, and inconclusive based on various methodological concerns, including biases associated with defining the start of follow-up as well as testing bias.

In an attempt to gain further insight, Heemskerk-Gerritsen and colleagues throughout the Netherlands examined prospective data on the efficacy of BRRM when compared with surveillance on breast cancer risk and mortality in healthy BRCA1 and BRCA2 mutation carriers. They followed 570 healthy female mutation carriers (405 BRCA1, 165 BRCA2) who were selected from the institutional Family Cancer Clinic database. Eventually, 156 BRCA1 and 56 BRCA2 mutation carriers underwent BRRM. The effect of BRRM vs surveillance was estimated using Cox models.

During 2037 person-years of observation (PYO), 57 breast cancer cases occurred in the surveillance group vs 0 cases during 1379 PYO in the BRRM group

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(incidence rates, 28 and 0 per 1000 PYO, respectively). In the surveillance group, four women died of breast cancer, while one woman in the BRRM group presented with metastatic breast cancer 3.5 years after BRRM (no primary breast cancer), and died afterward, yielding a hazard ratio of 0.29 (95% confidence interval 0.02-2.61) for breast cancer-specific mortality.

The authors concluded that in healthy BRCA1/2 mutation carriers, BRRM when compared with surveillance reduces BC risk substantially. Nonetheless they point out that a longer follow-up is warranted to confirm the observed survival benefit.

## COMMENTARY

This article examined the risk reduction and mortality from breast cancer for a group of healthy women known to be mutation carriers for BRCA1 and BRCA2. As noted, the investigators concluded from this prospective analysis, the group of women who elected BRRM had a "substantial breast cancer risk reduction" when compared with those who chose active surveillance. The data support the conclusions derived from retrospective studies and from projections based on mathematical models with simulated cohorts, yielding maximal survival probability for BRCA1/2 mutation carriers undergoing both BRRM and RRSO.[7-9]

In the general population, breast cancer incidence increases with aging and the same is more striking for the carriers of these mutations.[10] *(See Table.)*

Although the current paper provides a compelling argument for the efficacy of BRRM, there are two significant concerns: the relative short follow-up noted by the authors, but more importantly the surveillance group is substantially older with 42% aged 40 and older while only 25% of those selecting BRRM were 40 and older. The efficacy of BRRM over surveillance is supported by this prospective study, but comparability in age groups for both is necessary to set aside this potential bias. ■

**Table: Cancer by Age (Proportion, %)**

| | ≤ 45 years | ≥ 70 years |
|---|---|---|
| BRCA1 alone | 20-40% | 35-85% |
| BRCA2 alone | 10-25% | 45-85% |
| BRCA1 and BRCA2 | 15-30% | 35-65% |

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# ABSTRACT & COMMENTARY

## First-line Lenalidomide for Elderly CLL Patients

*By William B. Ershler, MD*

SYNOPSIS: In a single institutional study (M.D. Anderson), 60 older patients with chronic lymphocytic leukemia were treated with lenalidomide. Thirty-five of the 60 patients had a response lasting > 36 months, and compared with those who did not have such a durable response, those who did had lower pretreatment ß-2 microglobulin levels and were more

likely to have favorable cytogenetics. Lenalidomide treatment was associated with improvement in circulating immunoglobulin levels and T-lymphocyte numbers.

SOURCE: Strati P, et al. Lenalidomide induces long-lasting responses in elderly patients with chronic lymphocytic leukemia. *Blood* 2013;122:734-737.

Recent data from NCI SEER indicate the median age at diagnosis for chronic lymphocytic leukemia (CLL) is 71 years.[1] Whereas a wide range of therapeutic approaches have been generally recommended for newly diagnosed patients ranging from observation alone, to single or combination chemotherapy, to allogeneic stem cell transplantation under various circumstances, optimal initial therapy for older CLL patients has yet to be established.[2] Agents such as chlorambucil, fludarabine, and bendamustine have been explored with reasonably good response rates and tolerability. Recently, lenolidomide has proven effective for patients with both relapsed/refractory disease[3,4] and in the first-line setting.[5]

To examine the safety and efficacy of single-agent lenolidomide in elderly patients with CLL, Strati and colleagues from the M.D. Anderson Cancer Center performed a Phase 2 trial in which they enrolled 60 treatment-naïve elderly CLL patients (median age 71 years, range 66-85 years). Treatment consisted of lenolidomide (5 mg, orally) administered continuously. After 2 months, treatment doses were escalated by 5 mg to a maximum dose of 25 mg/day. Patients remained on treatment until there was evidence for disease progression.

At a median follow-up of 4 years, time-to-treatment failure had not been reached and overall survival was 82%. Thirty-five (58%) patients had a response lasting > 36 months (long-term responders [LTRs]) and the clinical features and results for these patients were compared to those who did not meet criteria for LTR (short-term responders [STRs]). Among the LTRs, the best responses consisted of 25 (71%) complete remissions and 10 (29%) partial remissions. In addition to clinical responses, an increase in IgA, IgG, and IgM levels of > 50% from baseline was reported in 61%, 45%, and 42% of LTRs. Normalization in the percentage of CD4 and CD8 T cells and overall T-cell numbers were observed in 48%, 71%, and 99% of LTRs. Compared with STRs, LTRs had lower baseline plasma levels of ß-2-microglobulin, were more likely to have trisomy 12, and less likely to have deletion 17p. The median daily dose of lenalidomide was 5 mg (range, 2.5-10 mg).

## COMMENTARY

In an earlier study out of Toronto, Chen and colleagues[5] used lenalidomide as initital treatment for patients with CLL. The plan was to use lenalidomide at 10 mg/d for 21 days of a 28-day cycle with weekly 5 mg dose escalations to a target of 25 mg. However, they encountered severe toxicities (tumor lysis, fatal sepsis) in the first two patients enrolled. The study was halted and the protocol amended to a more conservative regimen: starting dose of lenalidomide 2.5 mg with monthly escalations to a target dose of 10 mg. Twenty-five patients were enrolled on the amended protocol. No further tumor lysis events were reported. Tumor flare was common (88%) but mild. Grade 3 to 4 neutropenia occurred in 72% of patients, with only five episodes of febrile neutropenia. The overall response rate was 56% (no complete responses). Although rapid peripheral lymphocyte reductions were observed, rebound lymphocytoses during the week off-therapy were common.

In the current M.D. Anderson trial, 40% of those considered LTRs needed a dose reduction within 18 months of treatment, and this was most commonly due to hematologic toxicity. Of the 35 LTRs, 10 discontinued lenalidomide for a variety of reasons including neurotoxicity (n = 2), deep vein thrombosis (n = 1), infection (n = 1), weight loss (n = 1), thrombocytopenia (n = 1), and the development of squamous cell skin cancer (n = 1). Only one patient discontinued because of evidence for disease progression, and that was after 43 months of treatment.

Thus, lenalidomide was shown to be effective in the initial management of elderly patients with CLL. A number of questions remain to be addressed regarding the optimal use of this drug, including when to start treatment and at what dose. For patients with more favorable presentations (e.g., asymptomatic, favorable biochemical markers and cytogenetics, etc.), delaying treatment until clear progression is evident remains a reasonable approach, and initial treatment at 2.5 mg/day may also prove to be effective and with less toxicity. These, of course, are questions to be most satisfactorily addressed by clinical trial. ■

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## ABSTRACT & COMMENTARY

# A Multimodality Approach to the Initial Management of Stage IV Rectal Cancer

***By Bindu Kanapuru, MD***
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**Dr. Kanapuru reports no financial relationships relevant to this field of study.**

SYNOPSIS: In this Phase 2, single-arm, multicenter clinical trial conducted in the Netherlands, 50 patients with metastatic rectal cancer were treated with 5 days of 5 Gy RT followed by six cycles of intravenous bevacizumab (7.5 mg/kg) and oxaliplatin (130 mg/m$^2$) on D1 and capecitabine (1000 mg/m$^2$) orally on D1-D14. Thereafter, resection of the primary tumor and metastatic disease (when possible) was undertaken. Efficacy and tolerability was assessed as percentage of patients who underwent radical resection, survival at 2 years, and recurrence rates, as well as treatment-related toxicity. Nearly three-fourths of the patients underwent curative resection, and 2-year overall survival was 84%. Treatment was well tolerated with no treatment-related deaths.

SOURCE: van Dijk TH, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol* 2013;24:1762-1769.

The best treatment for primary metastatic rectal cancer is not established. In selected patients undergoing resection of metastatic disease, studies have shown prolonged survival and, for some, potential cures. But such an approach is often difficult because primary rectal tumors are frequently locally advanced and require prompt treatment. Neoadjuvant chemotherapy or chemo radiotherapy (RT) has been used to potentially downstage tumors and convert unresectable disease to resectable. However, the prolonged periods without systemic therapy for those with metastatic disease and the added toxicity of radiation may reduce the benefits of surgical resection in patients who are known to have metastatic disease at presentation. Short-course RT has been shown to produce similar rates of distant failure, overall survival, and late radiation toxicity when compared to long duration chemo-RT. However, chemotherapy with short-course RT has not yet been tested.

In this study, to overcome the logistical issues in treatment sequence, the investigators used a preoperative short-course pelvic radiotherapy including five fractions of 5 Gy each (5 × 5 Gy), followed by capecitabine and oxaliplatin (CapeOx) given in combination with bevacizumab prior to surgical resection. Systemic chemotherapy with bevacizumab/CapeOX was started 2 weeks after completion of short-course RT. The RT was delivered by linear accelerator and the clinical target volume included the primary tumor, mesorectum, and internal iliac nodes. Six to 8 weeks after completion of chemotherapy, total mesorectal resection of the primary tumor was performed. Surgical treatment of metastases included partial liver or lung resection, radiofrequency ablation (RFA) of liver metastases, or a combination of resection and RFA.

Fifty patients ≥ 18 years of age with resectable hepatic or lung metastasis with adequate organ function and hematological parameters were enrolled from seven centers in the Netherlands in this single-arm, Phase 2, open-label study between April 2006 and December 2010. Patients who received previous pelvic radiotherapy and 5 fluorouracil-based chemotherapy for any disease were excluded. Baseline imaging of the primary tumor and preoperative assessment was by CT or MRI. Distant metastatic disease at baseline, after two cycles, and upon completion of therapy was assessed by CT imaging. Following completion of therapy, patients were followed every 3 months with clinical examination, carcino-embryonic antigen (CEA) levels, and imaging studies. The primary endpoint was the percentage of patients receiving radical surgical treatment of all tumor sites (R0). Secondary endpoints were 2-year survival, 2-year recurrence rate, and treatment-related toxicity. Pathologic complete response after neoadjuvant treatment (ypCR) was defined as the absence of residual tumor cells in the primary tumor and lymph node specimens (ypT0N0). Down staging was assessed by comparing pathologic stage (ypT) with baseline clinical T-stage. Radical (R0) RFA was assessed by 1-week post-procedural CT scan with an ablation

zone with tumor-free margins ≥ 5 mm. Toxicity was graded according to NTCAE version 3.0 and surgical complications were also compiled.

All patients had an ECOG performance status ≤ 1. Eighty-four percent of the patients had liver metastasis and 64% had cT3N1-2 disease. All 50 patients received RT and 49 patients received preoperative chemotherapy, with 84% of the patients receiving all six cycles of the planned therapy. Ninety-six percent of the patients (48/50) were scheduled for surgery by curative intent, and 72% of patients underwent R0 resection of all surgical sites. Ninety percent of the patients were able to undergo resection of their primary rectal cancer. Pathological complete response was seen in 26% of the patients. Simultaneous resection of primary and metastatic disease was carried out in 26 patients. There were no grade 3 or 4 toxicity-related events observed before or after RT. Six percent of the patients discontinued bevacizumab, and the most common grade 1 or 2 toxicities observed were neuropathy, fatigue, and nausea. The median time from completion of chemotherapy to surgery was 39 days. No patient deaths were observed within 90 days after surgery. The 2-year overall survival rate was 80% (40 of 50 patients) in the intent-to-treat group, and the 2-year recurrence rate after R0 resection was 64% (23 of 36 patients). Median time to recurrence was 13 (range 7-20) months.

## COMMENTARY

The authors have clearly demonstrated that short-course RT followed by chemotherapy is a safe and efficacious therapy for patients with metastatic rectal cancer. The complete pathological responses seen in this trial (26%) are similar to response rates observed in patients receiving concurrent chemo-radiotherapy regimens. In addition, 47% down staging was observed from clinical to pathological stage similar to what has been observed with long-course RT. The 2-year recurrence rates and survival rates were also comparable to other studies enrolling patients with similar disease severity.

However, although the rate of surgical morbidity was comparable to other studies, the need for additional surgical intervention for postoperative complications was more frequent. The Hartmann procedure was the most common surgical procedure performed (53%) rather than immediate anastomosis to avoid complications. The rates of sphincter preservation were not reported as an endpoint.

This was a relatively small, single-arm study and, thus, the generalizability of results is limited. Yet, this aggressive approach for the management of metastatic rectal cancer was shown to be feasible and the results are clearly sufficient to form a basis for a randomized controlled trial in patients with resectable metastatic disease. ■


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# ABSTRACT & COMMENTARY

# What is the Impact of Pediatric Cancer Care on Future Fertility in Female Survivors?


***By Robert L. Coleman, MD***

*Professor, University of Texas; M.D. Anderson Cancer Center, Houston*



**Dr. Coleman reports no financial relationships relevant to this field of study.**

*This article originally appeared in the September 2013 issue of* **OB/GYN Clinical Alert.**



SYNOPSIS: Women undergoing pediatric cancer care are significantly more likely than their siblings to have clinical infertility (≥ 12 months of non-conception despite desired attempts) and total infertility (clinically infertile women who also reported ovarian failure defined as never initiating menstruation or no periods 5 years before baseline questionnaire). Although infertile cancer survivors were no more likely to seek professional help for conception than their siblings, they were significantly less likely to receive drugs to assist with conception. They also had an increased time to achieve pregnancy. The report provides the first large-scale, comprehensive survey of infertility in childhood cancer survivors.

SOURCE: Barton SE, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: A report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol* 2013;Jul 12 [Epub ahead of print].

Previous studies have shown decreased pregnancy rates and early menopause in female cancer survivors; however, infertility rates and reproductive interventions have not been studied. This study investigated infertility and time to pregnancy in female childhood cancer survivors, and analyzed treatment characteristics associated with infertility and subsequent pregnancy. The primary dataset was developed by querying the Childhood Cancer Survivor Study (CCSS), a multinational (United States and Canada) cohort study enrolling 5-year cancer survivors who were younger than 21 years at the time of diagnosis between Jan. 1, 1970, and Dec. 31, 1986, and a sibling control group. Women aged 18-39 years who had ever been sexually active provided medical and reproductive data via a baseline questionnaire and underwent quantification of alkylating agent and radiation therapy exposure. The authors analyzed self-reported infertility, medical treatment for infertility, time to first pregnancy in survivors and siblings, and the risk of infertility in survivors by demographic, disease, and treatment variables. Overall, 3531 survivors and 1366 female sibling controls were evaluated. Compared with their siblings, survivors had an increased risk of clinical infertility (relative risk [RR], 1.48; 95% confidence interval [CI], 1.23-1.78; $P < 0.0001$), which was most pronounced at early reproductive ages (e.g., age 24 years; RR, 2.92; 95% CI, 1.18-7.20; $P = 0.02$, in participants ≤ 24 years). Despite being equally likely to seek treatment for infertility, survivors were significantly less likely than were their siblings to be prescribed drugs for treatment of infertility (RR, 0.57; 95% CI, 0.46-0.70; $P < 0.0001$). Increasing doses of uterine radiation and alkylating agent chemotherapy were strongly associated with infertility. Although survivors had an increased time to pregnancy compared with their siblings ($P = 0.032$), 292 of 455 participants (64%) with self-reported clinical infertility ultimately achieved a pregnancy. These data provide more comprehensive understanding of infertility after successful pediatric cancer care and avenues for counseling and decision-making about future conception attempts and fertility preservation.

## COMMENTARY

Successful care in pediatric cancers has been a remarkable achievement over the past several decades. Overall, long-term survivorship is now the norm and many of these patients (male and female) have interest in achieving pregnancy. The CSS is a comprehensive, multinational, cohort study that enrolled patients with pediatric cancers and their unaffected siblings (controls) to evaluate interventions and outcomes.[1] This latest report targeted reproductive history and fertility to better define expectations from treatment and significantly enhance the limited data on the topic to provide better counseling opportunities. Eligible malignancies were leukemia, CNS cancer, Hodgkin's lymphoma, non-Hodgkin lymphoma, Wilms' tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors. Many of these malignancies are treated with partial or total body radiation and/or the use of alkylating agents, both of which have been linked to reproductive failure and infertility.[2] By using a sibling cohort, the investigators were better able to estimate relative infertility in affected individuals by providing some control of shared familial and environmental risks. Previous studies of the participants in the CSS have documented no significant clinical or demographic differences in the cohorts.

Overall, the data are in line with expectations from these types of therapy. It has been known for many years that the ovaries are sensitive to radiation and fail at a higher rate than expected, even when transposed or blocked during therapy.[2] In addition, alkylating agents are known to have a dose effect on ovarian failure, which was assessed in the current study by creating an index of total exposure based on dose, frequency, and number of courses of chemotherapy involving these agents. However, the new data demonstrate that the impact of therapy on clinical infertility is greatest early on (≤ 24 years of age) and diminishes over time, despite remaining more common in survivors compared to their siblings. This was manifested by increasing time to first pregnancy despite the similar rates of infertility specialist referral. Of some surprise was the lower use of fertility-enhancing drug therapies. The data did not address causes or reasons for the variance, but it was considered that there might be reluctance to use these agents due to subsequent cancer/medical risk or low confidence they would work. Although infertility care is much better today than during the time of exposure for the cohort (about a decade ago), these observations serve to enhance the discussions of health care providers with patients and caregivers in addressing the topic of fertility following therapy.

The topic is of increasing importance, as more and more cancer survivors are making it to the age of majority and are as interested in opportunities for childbearing as noncancer patients. For women who have already begun to ovulate and in whom preservation is still of interest ahead of planned additional therapy, many new options are available

such as cryopreservation of oocytes, embryos, and even unstimulated ovarian cortical tissue. The American Society of Clinical Oncology recently updated its guidelines of fertility preservation, which will bring the discussion to the forefront of treatment planning.[3] ■


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## ABSTRACT & COMMENTARY

# Stopping Imatinib: When is Enough Enough?

*By William B. Ershler, MD*


**SYNOPSIS:** Imatinib therapy was discontinued in 40 patients who had sustained undetectable *BCR-ABL* transcripts for 2 or more years, and close follow-up revealed approximately 50% remained with undetectable disease off treatment at 24 months. For those who developed evidence for recurrence, imatinib reinduced deep molecular responses. However, using a highly sensitive research assay, patients in treatment-free remission still have detectable *BCR-ABL* DNA. Thus, continued vigilance to diagnose and treat early relapse remains clinically relevant, even for those off therapy for several years.


**SOURCE:** Ross DM, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: Results from the TWISTER study. *Blood* 2013;122:515-522.

Imatinib treatment for chronic myelogenous leukemia (CML) commonly induces a major molecular response (MMR) with very low levels of *BCR-ABL* transcripts (minimal residual disease, MRD) detected by sensitive RT/PCR assays. In approximately 40% who receive the drug for 5 or more years, the *BCR-ABL* transcript is undetectable (UMRD).[1,2] Yet, prior studies have shown that stopping imatinib in patients with UMRD is typically followed by the reappearance of detectable *BCR-ABL*.[3,4] It has been speculated that for those with UMRD evident for several years, stopping may be possible without subsequent molecular relapse.[5] In fact, in the French Stop Imatinib (STIM) study, 100 imatinib-treated CML patients with sustained (> 2 years) undetectable disease were taken off drug. After a 12-month follow-up, approximately 40% of patients remained with undetectable *BCR-ABL* transcripts, raising the hopeful expectation that for certain individuals the disease might indeed be cured by imatinib.[5]

In the current study, Ross and colleagues report findings from the Australasian Leukemia & Lymphoma Group TWISTER study. They conducted a prospective clinical trial of imatinib withdrawal in 40 chronic-phase CML patients on imatinib for a minimum of 3 years who had sustained undetectable minimal residual disease (UMRD) by conventional quantitative polymerase chain reaction (PCR) for at least 2 years. Patients stopped imatinib and were monitored regularly for molecular relapse. After 24 months, the actuarial estimate of stable treatment-free remission (TFR) was 47.1%. Most relapses occurred within 4 months of stopping imatinib, and no relapses beyond 27 months were seen. In the 21 patients treated with interferon before imatinib, a shorter duration of interferon treatment before imatinib was significantly associated with relapse risk, as was slower achievement of UMRD after switching to imatinib. Using a highly sensitive, patient-specific *BCR-ABL* DNA PCR assay, as previously reported from this group,[6] showed persistence of the original CML clone in all patients with stable UMRD, even several years after imatinib withdrawal. For those who did relapse, recommencement of imatinib therapy was generally effective in producing deep molecular responses. Further, none of the patients had developed *BCR-ABL* mutations (median follow-up, 42 months).

## COMMENTARY

This is an important contribution because in a prospective study it confirms the conclusions from the STIM trial that imatinib therapy may be discontinued safely in those with stable UMRD, with the provision that subsequent management would include frequent and sensitive molecular monitoring and early rescue if molecular relapse occurs. Important features include the reassurance that all patients who experienced molecular relapse remained sensitive to imatinib therapy. Another important finding was the demonstration that peripheral blood was equally effective to bone marrow sampling in predicting or identifying early relapse. However, the demonstration of patient-specific, very low levels of *BCR-ABL* DNA transcripts (using a research methodology not available outside the research setting) in all patients with traditional laboratory-diagnosed UMRD was somewhat disconcerting. This would imply the persistence of the leukemia

clone, even without evidence for active proliferation based on the traditional RT/PCR methodology and raises a specter of caution concerning late relapse, even in patients off therapy for several years.

Beyond imatinib, second- and third-generation tyrosine kinase inhibitors are now currently available and are used by many as first-line treatment based on their superiority in inducing more rapid and deeper molecular responses.[7,8] Sustained response to these agents are likely to produce at least comparable results to those demonstrated in the STIM and TWISTER studies, raising once again that hopeful expectation that the leukemia clone may be eradicated completely. However, patients and clinicians await the results from similarly conducted clinical trials examining the potential for these newer agents to produce sustained undetectable disease years after the discontinuation of therapy. ■

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## Continuing Education Questions

**1. The study comparing breast cancer risk in healthy women who carry germ-line BRCA1/2 mutations is notable for its:**

a. retrospective analysis.
b. prospective, observational design.
c. randomized, prospective design.
d. mathematical modeling analysis.

**2. In the CLL study of initial lenalidomide treatment, the median daily dose of lenalidomide prescribed for those considered long-term responders was:**

a. 2.5 mg.
b. 5 mg.
c. 10 mg.
d. 25 mg.

**3. In combined short-course RT, chemotherapy, and radical surgery trial for patients presenting with metastatic rectal cancer, the simultaneous resection of primary and metastatic disease was attempted at which point in the treatment sequence?**

a. Initially, before short course RT and chemotherapy
b. After short-course RT, before systemic chemotherapy
c. After systemic chemotherapy, before short-course RT
d. After short-course RT and systemic chemotherapy

**4. Which of the following best describes the Childhood Cancer Survivor study?**

a. It was a randomized, controlled, cohort trial.
b. The primary study cohort were cancer patients under active treatment.
c. Infertility was classified by two definitions — clinical and total infertility.
d. Dosing of non-alkylating agents was indexed to measure effect on future fertility.

**5. Current data from both the STIM and TWISTER studies would suggest that of patients treated with imatinib for 3 or more years who have had demonstrable deep molecular responses (i.e., undetectable *BCR-ABL* transcripts by RT/PCR), approximately what percent will remain with undetectable disease 2 years after discontinuation of imatinib?**

a. 90%
b. 70%
c. 40%
d. 5%

[IN FUTURE ISSUES] Sorafanib + TACE for HCC

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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## Once-daily Tadalafil for ED: Efficacy and Safety

**Source:** Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

## Psychological Disorders: How to Give Patients What They Want and What They Need

**Source:** McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

## Reducing Stroke Risk After TIA or Minor Ischemic Stroke

**Source:** Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

## Long-term Mortality Among Adults with Asthma

**Source:** Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

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## Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

**Source:** The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

## New Hope for Hepatitis C Patients

**Source:** Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

# Do Statins Prevent Parkinson's Disease?

***In this issue:*** Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

## Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

## Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

## AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

## FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■