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A monthly update of developments in cancer treatment and research [ALERT]

ILLUSTRATIVE CASE SERIES

Case Management: Acute Promyelocytic Leukemia

By Jerome W. Yates, MD

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

A 44-year-old male patient is seen in the emergency room because of intractable nose bleed, hematuria, and ecchymoses — all first noted within the past 48 hours. Previously he had been well, without known medical illness, and was taking no prescription drugs. He had no prior history of bleeding, nor had he any family member with bleeding disorder. He had no knowledge of exposure to toxic chemicals or drugs and had not traveled or eaten any unusual foods over the past year. He was not experiencing pain, confusion, or shortness of breath, although he had had diarrhea over the past week and noted fatigue and decreased appetite.

Physical exam revealed persistent posterior nasal bleeding and ecchymoses over the arms and trunk. He was afebrile and blood pressure was 110/72, pulse 88, and regular and oxygen saturation was 98% on room air. There was no palpable lymphadenopathy splenomegaly or hepatomegaly. Abdomen was soft without mass or tenderness.

Laboratories in the emergency room indicated a hemoglobin of 10.1 g/dL, a white blood count of 8,000/cu mm, and a platelet count of 78,000/cu mm. White blood differential revealed 11% neutrophils, 3% band forms, 4% lymphocytes, and approximately 80% large hypergranular cells interpreted by the laboratory technician as promyelocytes with irregular appearing primary azurophilic granulocytes and Auer rods. Serum chemistries were essentially within normal limits. Prothrombin time and partial throm-

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boplastin times (PT and PTT) were both > 2 times the normal limit.

DISCUSSION

Although by no means confirmed, the patient's diagnosis is most likely the promyelocytic variant of acute myelogenous leukemia. This scenario is one of the true "oncologic emergencies" because failure to institute prompt therapy can result in rapid demise, particularly from hemorrhage into the central nervous system. In fact, this is a situation in which you must rely on clinical judgment. Order confirming laboratory studies but do not wait for the results of those studies before initiating therapy.[1]

Acute promyelocytic leukemia (APL) accounts for approximately 10% of acute leukemia in adults and is somewhat more common in children. It results from a balanced reciprocal translocation between chromosomes 15 and 17, producing a fusion transcript of the *PML* and *RAR-a* genes.[2,3] Leukemic cells of this type have the unique ability to undergo differentiation with exposure to either retinoic acid or arsenic trioxide.

In the current case, the initial approach would be to review the peripheral blood smear with an experienced hematopathologist, if available. Bone marrow aspirate and biopsy should also be obtained and should include both cytogenetic and molecular studies, if this can be arranged in a timely fashion, but should not delay therapy.

Response rates in APL are excellent. However, a great risk for catastrophic outcomes remains without aggressive early management. In the case under discussion, the white count of > 10,000 places the patient in the "high-risk" group,[4] and treatment with all-trans retinoic acid (ATRA) (45 mg/m^2 in divided doses) should be initiated very early, even while in the emergency room, if possible. For those in the high-risk category, the addition of an anthracycline concurrent with ATRA is advisable to reduce the risk that ATRA alone might be associated with additional leukocytosis. However, for those with low or intermediate risk, ATRA alone is recommended for a few days prior to additional chemotherapy.

Additional, aggressive, early supportive measures can be life-saving. Platelet counts should be maintained above 30,000/cu mm and cryoprecipitate administered to maintain the fibrinogen level above 150 mg/dL. If ATRA is administered promptly, there is no clear benefit for the use of heparin, except perhaps for those who have recognized deep vein thrombosis or who are on antifibrinolytic therapy. The placement of a central line and lumbar puncture, typical early measures in the management of acute leukemia, should be delayed until adequate coagulation parameters are reached.

For patients with high-risk APL, particularly for those with presenting WBCs of > 30,000/cu mm, therapy may result in what has been termed APL differentiation syndrome,[5] manifested predominantly by pulmonary insufficiency; the incidence of this may be reduced with preemptive corticosteroids.

Although deaths continue to occur in the early phase of management of APL, for those in whom coagulation is promptly controlled and full treatment (induction, consolidation, and maintenance) administered, long-term, disease-free outcomes are likely. Clinical trials are currently addressing the optimal management for those with high-risk disease to determine the most effective combinations of ATRA, arsenic trioxide, and anthracycline in initial therapy, as well as those or other agents in consolidation or maintenance. Nonetheless, prompt and aggressive early diagnosis and management are critical in achieving a successful outcome for these patients. ■

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RAPID REVIEW

Bendamustine for the Treatment of Indolent Non-Hodgkins Lymphoma and Chronic Lymphocytic Leukemia

Guest Discussant: Robert G. Fenton, MD, PhD
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Dr. Fenton reports no financial relationships relevant to this field of study.

Bendamustine was first synthesized in 1963 in East Germany, but its clinical development as an antineoplastic agent really began after the fall of the Iron Curtain. Bendamustine combines a mechlorethamine group, similar to other alkylating agents such as cytoxan and chlorambucil, with a benzimidazole ring, similar to some purine analogs such as 2-chlorodeoxyadenosine (although no evidence for an anti-metabolite function has been demonstrated). In-vitro experiments suggest that bendamustine induces more DNA adducts and strand breaks than other alkylating agents, and that DNA lesions are repaired with slower kinetics.[1] In early clinical studies, non-cross resistance to bendamustine was observed in chlorambucil-resistant CLL and chemotherapy-refractory NHL[2] and, during the past decade, bendamustine has demonstrated potent activity as a single agent, and in combination, for low-grade B-cell neoplasms. Some of the most relevant studies will be reviewed here.

BENDAMUSTINE IN NHL

Single-agent bendamustine was tested in 100 heavily pretreated (median of two previous regimens), rituximab-refractory indolent NHL patients.[3] The patients (ages 31-84) received bendamustine 120 mg/m^2 day 1 and day 2 every 21 days for 6-8 cycles. The overall response rate (ORR) was 84%, with 29% CR and a progression-free survival (PFS) of 9.7 months. Toxicities were mainly myelosuppression, but also included fatigue, nausea, and xerostomia. This study led to FDA approval of bendamustine for second-line treatment of indolent NHL.

The striking activity of bendamustine as a single agent led to investigations of its activity in combination with rituximab. The German group treated 63 patients with relapsed or refractory low-grade NHL (58% with high risk FLIPI scores) with rituximab 375 mg/m^2 on day 1 and bendamustine 90 mg/m^2 day 2 and day 3 on a 28-day schedule.[4] The median age was 63, and toxicities included 16% grade 3-4 neutropenia and grade 1 nausea in 102 or 136 cycles. The ORR to the BR regimen was 90%, with 60% CR. The subgroup of patients with mantle-cell lymphoma (MCL) had an ORR of 75%, with 50% CR. The median PFS for all patients was 24 months, and 18 months for the MCL group. These results prompted an identical confirmatory study in the United States. Sixty-six patients with a median age of 60 were treated with BR.[5] The results were amazingly concordant with the German study, with an ORR of 92%, 55% CR, and a PFS of 23 months. Outcomes were similar for the indolent NHL and mantle-cell histologies. Toxicity was mainly hematologic (36% grade 3-4 neutropenia). The overall survival has not been reported for either study.

In a phase-II study of 54 patients with relapsed/refractory NHL and CLL (ages 40-83), mitoxantrone (10 mg/m^2 day 2) was added to bendamustine (90 mg/m^2 day 1 and day 2) and rituximab (375 mg/m^2 on days 8, 15, 22, 29), followed by BM without rituximab for an additional five cycles.[6] The ORR was 96%, with 41% CR and a PFS of 17 months in CLL and > 27 months in NHL (follicular lymphoma, mantle-cell lymphoma, and marginal zone lymphoma). While this BMR regimen is active, a randomized study would be required to determine if mitoxantrone adds anything to the BR regimen.

UNPUBLISHED DATA FOR BENDAMUSTINE TREATMENT OF NHL

A German cooperative group study recently performed a randomized study of 513 patients randomized to R-CHOP or BR for the first-line treatment of MCL and follicular lymphoma (FL). The data strongly favor the BR regimen in PFS (55 months vs. 35 months), CR (40% vs. 30%). In FL, the PFS was 47 months for R-CHOP and has not yet been reached for BR. The BR regimen was associated with less alopecia, neupogen requirement, stomatitis, and sepsis, and was felt to potentially be an

excellent treatment option for elderly patients with MCL.

Bortezomib has significant single-agent activity in MCL and some activity in FL. ECOG performed a phase-II study of bendamustine (90 mg/m^2 days 1 and 2) with standard doses of bortezomib and rituximab (BVR regimen). The ORR was 80% and PFS at one year was 74%. The Vertical study treated 65 FL patients with BVR in which the bortezomib was administered once a week for four weeks (instead of the usual days 1, 4, 8, and 11 every 21-day schedule), on a 35-day treatment cycle. The ORR of evaluable patients is 85%. Note that as in MM, there appears to be significantly less peripheral neuropathy when bortezomib is used on a once-a-week schedule.

Important future trials will include a planned phase-III comparison of the very active FCR (fludarabine, cyclophosphamide, rituximab) regimen with BR in the first-line treatment of NHL patients. It will also be of great interest to determine the activity of BVR in MCL as compared to HyperCVAD +R with or without bortezomib. For elderly patients, the Ara-C/MTX cycles of HyperCVAD may be replaced with bortezomib to generate a regimen that can be tolerated by patients with co-morbid medical conditions. The ability to mobilize adequate stem cells for auto-transplant after bendamustine treatment, and the incidence of drug-induced myelodysplastic syndrome (MDS), remain to be fully explored.

BENDAMUSTINE IN CLL

Two phase-I/II studies from Europe demonstrated promising activity of single-agent bendamustine in heavily pretreated and refractory CLL.[7,8] The MTD was either 70 or 100 mg/m^2 days 1 and 2, when given on a 3-4 week cycle. Response rates were approximately 50% with some CRs. Dose-limiting toxicities were myelosuppression and infection. Based on these data, the German CLL Study Group performed a prospective, multicenter, randomized trial of bendamustine (100 mg/m^2 days 1 and 2) vs. oral chlorambucil (0.8 mg/kg on days 1 and 15, every 28 days) in 319 previously untreated CLL patients < 75 years of age.[9] Bendamustine was more active, with a RR of 68% vs. 31% for chlorambucil ($p = 0.0001$) and improved PFS (21.6 vs. 8.3 months; $p = 0.0001$). Bendamustine induced more grade 3-4 neutropenia (23 vs. 10%) but was otherwise well tolerated. This study led to FDA approval of bendamustine for the first-line treatment of CLL. However, the choice of chlorambucil as the control arm does not conform to the modern use of fludarabine as the standard first-line therapy, which is also known to be significantly more active than chlorambucil.

The German CLL Study Group then added rituximab (375 mg/m^2 cycle 1, increased to 500 mg/m^2 on subsequent cycles) to bendamustine (70 mg/m^2 days 1 and 2) given every 28 days for up to six cycles. One hundred seventeen patients were treated in this phase-II study, with a 90% RR that included 33% CRs. Seventy-five percent of patients were still in remission at 18 months.[10] This group is now recruiting patients to a phase-III study (CLL10) comparing FCR with BR as a primary therapy for CLL.

In conclusion, bendamustine has demonstrated significant activity for the treatment of low-grade B-cell malignancies. Its future role in the treatment of FL, MCL, and CLL will await the results of ongoing phase-III studies comparing BR and BVR to more standard regimens in each disease. It appears likely that given its predictable toxicity profile and induction of durable remissions will render it an important agent for treating frail, elderly patients who are not candidates for more aggressive therapies. ■

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ABSTRACT & COMMENTARY

Transplantation for Older Adults with AML and MDS

By Andrew S. Artz, MD

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

Synopsis: *AML and MDS are primarily diseases of older adults with poor long-term outcomes. McClune and colleagues evaluated data from the Centers for International Marrow and Stem Cell Transplantation Registry (CIBMTR) to assess outcomes of adults 40 years or older undergoing HCT for AML in CR1 or MDS after reduced intensity or non-myeloablative regimens. They found 1,080 patients with AML or MDS. The two-year survival rate was over 30%. Older age did not influence overall survival, disease-free survival, non-relapse mortality, or the incidence of acute graft-versus-host disease. Only 10%-12% were 65 years and older. Age alone should not represent a contraindication to considering allogeneic hematopoietic cell transplantation for AML and MDS patients 40 to 70 years of age.*

Source: McClune B, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older adults with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol.* 2010;28:1878-1887.

Allogeneic hematopoietic cell transplantation (HCT) has generally been recommended for younger adults with high-risk acute myeloid leukemia (AML) or high-risk myelodysplastic syndromes (MDS), and possibly for intermediate risk AML.[2,3] The significant treatment-related morbidity and mortality using high doses of chemotherapy and/or radiation historically limited HCT to younger and fit adults. AML and MDS predominantly occur in older adults, and the outcomes for adults 60 years and older with AML are dismal using standard chemotherapy alone. As a consequence, many investigators have explored HCT to abrogate these poor outcomes.

The chemotherapy and/or radiotherapy administered before hematopoietic cell infusion, known as the conditioning regimen, provides both an anti-leukemic effect and immunosuppression to facilitate donor cell engraftment. Over the past 10–15 years, the introduction of less intensive conditioning regimens has promoted expansion of HCT to older adults.

In this report, McClune and colleagues report data from the Centers of International Marrow and Stem Cell Transplantation Registry (CIMBTR). Patients aged 40 years or older undergoing Reduced Intensity (RIC) or Non-myeloablative (NMA) conditioning regimens were eligible. NMA regimens are based on the assumption that the conditioning regimen will lead to transient myelosuppression, defined as expected hematopoietic recovery without transplantation within 28 days. Donors were either related or unrelated, thus excluding cord blood units. Of the 1,080 patients, 545 had AML and 535 had MDS among 148 centers. For AML patients, 36% were 60 years and older, whereas 34% of the MDS patients were 60 years or older. Peripheral blood stem cells (PBSC) were much more common than bone marrow as a donor source. Neutrophil recovery was the same or better with advancing recipient age. The following transplant outcomes studied did not differ by age: acute graft-versus-host disease (aGVHD), chronic GVHD, non-relapse mortality, overall survival, and disease free-survival. NMA conditioning was associated with higher relapse rate. Disease-free survival was associated with older donor age.

Karnofsky performance status less than 80% (observed in approximately 16% of all recipients), HLA mismatched unrelated donor, and unfavorable karyotype impaired the two-year survival in multi-variable analysis.

■ COMMENTARY

In adults younger than 40 years of age, transplant is considered for those not falling in the good-risk cytogenetic categories of t(8;21), inversion(16), and t(15;17). The incidence of acute myeloid leukemia

and myelodysplastic syndromes are highly linked to advancing age. Advances in HCT, such as reduced intensity/non-myeloablative conditioning, more tolerable immunosuppression, and better supportive care have extended HCT to older adults. Still, the decision about whether older AML or MDS patients might benefit from allogeneic hematopoietic cell transplantation (HCT) has often been based on personal experience as most data derived from single-institutional feasibility studies with relatively short follow-up.

This report summarizes registry transplant data. These data are less influenced by selection bias related to a specific protocol, institution, or publication, and reflect actual practice and outcomes of reduced intensity and non-myeloablative conditioning for HCT for adults 40 years and older. Overall survival exceeded 30% at two years, which fares quite favorable to chemotherapy-alone approaches in these high-risk patients. Rates of graft-vs.-host disease, death from transplant, relapse, and overall survival did not differ markedly by age. These data provide reassurance, if not encouragement, that select older adults can achieve reasonable long-term outcomes with RIC/NMA transplantation.

Prior results show even at an institution with access to an HCT center, the uptake of HCT for older adults with AML in CR1 is very low. These data confirm low utilization, particularly among adults 65 years and older. Such patients reflect only 10%–12% of HCT in this series but well over 50% of cases of AML and MDS in adults 65 years and older. HCT outcomes in these older adults appear promising compared to the outcomes after standard chemotherapy on cooperative group clinical trials. One must recognize such patients are not directly comparable as patients receiving HCT primarily had controlled disease and likely excellent health enabling HCT to be offered. Confirming to what extent if any HCT benefits older patients will require further investigation. Nevertheless, these data support discussing HCT with older adults, particularly those with a performance status of 80% or greater. There appear to be limited numbers of patients 70 years and older limiting inferences about this age group.

More relapse occurred in the less intensive NMA conditioning approach compared to RIC. These data affirm a general HCT concept that more intensive conditioning reduces relapse at the expense of non-relapse mortality. Others have reported similar long-term survival among adults 60 years and older who underwent ablative conditioning. The optimal conditioning regimen for older adults remains unknown, and the authors correctly call for prospective studies.

Another major issue, as one considers older patients for HCT, relates to whether older siblings should serve as donors. This series shows a tendency for reduced use of related donors compared to unrelated donors with older recipient age. Presumably, health issues or age alone dissuaded transplant physicians from collecting older sibling donors, possibly contributing to the low rate of HCT in the oldest population. The age or health conditions of older sibling donors that increase complications from collection, or worsen recipient outcomes, is unknown.

Adults 40 years and older receiving reduced intensity or non-myeloablative conditioning for AML in CR1 or MDS have reasonable long-term overall survival. Among these patients, older age did not significantly influence acute graft-vs.-host disease, relapse, non-relapse mortality, or overall survival. Hematopoietic transplant should not be restricted based on age alone for MDS or AML in CR1, at least for those between 40 and 70 years. Further study will be needed to determine the risks and benefits of HCT compared to other approaches in older adults. ■

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ABSTRACT & COMMENTARY

Outcomes for Plasma Exchange to Treat TTP

By Andrew S. Artz, MD
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Dr. Artz reports no financial relationships relevant to this field of study.

Synopsis: *The risk of relapse after effective therapy with plasma exchange for thrombotic thrombocytopenic purpura (TTP) has not been well-characterized. Among 376 patients with an initial episode of TTP treated with plasma exchange, overall survival was around 68%, with a survival of 78% among the subset with idiopathic TTP. Survival did not differ on those having a low (< 10%) ADAMTS13 level. Relapse was greater for those with a low ADAMTS13 level at the time of presentation.*

Source: Hovinger J, et al. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood.* 2010;115:1500-1511.

The classic pentad of anemia, thrombocytopenia, neurologic abnormalities, renal abnormalities, and fever historically defined thrombotic thrombocytopenic purpura (TTP). TTP may be divided into idiopathic where no apparent underlying cause exists and secondary TTP related to a variety of disorders such as hematopoietic transplant, pregnancy, infection, drug, autoimmune or cancer. The realization of very low ADAMST13 levels in a substantial number of patients further clarified pathophysiology.

Plasma exchange has dramatically improved survival from around 10% to 70%–80%.[1] With an available treatment, the diagnostic criteria were loosened to require only microangiopathic hemolytic anemia and thrombocytopenia, leading to better recognition. More effective treatment has also presented the problem of relapse. In this paper, the authors report on the experience of the Oklahoma TTP registry to better characterize outcomes related to TTP.

The registry enrolled 398 consecutive patients with a diagnosis of TTP or HUS for whom plasma exchange (PEX) was requested in a 58 county region covering 2.3 million people. ADAMTS13 activity was measured by both quantitative immunoblotting and a fluorogenic assay. Of these, 376 met eligibility criteria. ADAMTS13 was available in 261 subjects. The median follow-up was 4.7 years. Of these, 148 of 361(41%) had idiopathic TTP. Among the 59% with secondary TTP, the most common causes in decreasing frequency were: drug, autoimmune, infection, bloody diarrhea, pregnancy, and stem cell transplant. The ADAMTS13 level was < 10% in 60 (23%) and > 10% in 201 (77%) patients. Of patients with low levels, most were in the idiopathic TTP group.

Overall survival was 69%. Survival was 80% for idiopathic TTP. Secondary TTP related to pregnancy/postpartum TTP fared extremely well, realizing survival of 93%. In contrast, less than 30% of patients after stem-cell transplant and infection-related TTP survived. Interestingly, survival did not change over the 20-year time period using plasma exchange. Relapse was significantly more common for patients with an ADAMTS13 < 10% among those surviving (and, thus, available for follow-up). The five patients who relapsed with baseline ADAMTS13 activity < 10% had unique characteristics. One was re-exposed to drug, leading to relapse, two patients had lupus with features overlapping with TTP, one patient had a low ADAMTS 13 that evolved over time, and another had a low level on one of the two assays.

Among the 47 surviving patients who had ADAMTS13 < 10%, only male sex predicted for relapse. Relapses in those with low ADAMTS13 activity occurred in the first year (63%), with a cumulative incidence of relapse at 7.5 years of 41%. In recent years, ADAMTS13 activity was periodically during remission for those with low activity at the time of presentation. Since December 2003, 13 patients with ADAMTS 13 activity < 10% received rituximab, generally for refractory or recurrent disease.

■ COMMENTARY

Oncologists are often asked to assist in the diagnosis and management of patients who have thrombotic thrombocytopenic purpura (TTP). The substantial improvement in mortality from plasma exchange demands early diagnosis and treatment and prompt initiation of treatment for TTP. Diagnosis only requires microangiopathic hemolytic anemia and thrombocytopenia. Data on outcomes from plasma exchange and relapse rates in responders have been limited. In this study, the authors were able to perform a population-based study derived from patients in a large area in Oklahoma, serviced by a single provider of plasma exchange. Over 20 years, 376 consecutive patients were studied who received TTP for an initial episode of TTP. Idiopathic TTP occurred in 41% whereas secondary TTP, related to a defined condition, accounted for the

majority. The survival rate of patients with idiopathic TTP was 80% similar to prior reports.[1] ADAMTS13 levels were available from more recent patients. Around half (47%) of the patients with idiopathic TTP had levels < 10% at presentation, although some patients with secondary TTP also had low levels. Thus, low ADAMTS13 is neither sufficient nor necessary for diagnosing idiopathic TTP. However, low ADAMTS13 level at presentation had a much higher risk of relapse compared to those with higher levels at presentation. Among those with low ADAMTS13 at presentation, 34% relapsed with a cumulative incidence of relapse at 7.5 years of 41%. Relapses were clustered within one year of initial diagnosis, indicating the need for close monitoring after remission, particularly during the first year. Interestingly, six patients received rituximab maintenance to avoid relapse, and none have relapsed. For those with ADAMTS13 levels > 10% at presentation, relapses rarely occurred; only 4% of 136 surviving patients relapsed, all within two years.

This large study of a large cohort of TTP patients treated with plasma exchange reveals that secondary TTP may be more common than idiopathic TTP. Reassuringly, plasma exchange enables reasonable survival of 80% for those presenting with idiopathic TTP. This study defies the common notion that low ADAMTS13 are pathognomonic for idiopathic TTP; some patients with low levels had secondary TTP and many patients classified as idiopathic TTP had levels > 10%. Lower levels of ADAMTS13 at presentation may predict for relapse once in remission. However, the exact monitoring strategy and intervention for this subset (e.g., rituximab) remain undefined. ■

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CME Questions

15. What outcome(s) were statistically significantly worse for older age among adults 40 years and older undergoing allogeneic hematopoietic cell transplantation for AML in CR1 or MDS?

a. Neutrophil engraftment was slower.
b. Disease-free survival was worse.
c. Overall survival at two years was worse.
d. The incidence of acute graft-versus-host disease was higher
e. None of these were worse

16. Initial therapy for patients with acute promyelocytic leukemia and frequent bleeding includes all of the following except:

a. All-trans-retinoic acid (ATRA)
b. Heparin
c. Cryprecipitate
d. Platelet transfusion

17. Low ADAMTS13 levels (< 10%) at the time of presentation predicted what among TTP patients treated with plasma exchange?

a. A significant risk of relapse of >30%.
b. High risk of cancer.
c. Recent use of Plavix.
d. Bleeding events.

Answers: 15. (e); 16. (b); 17. (a)

CME Objectives

Upon completion of this activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

[IN FUTURE ISSUES]

Fruits, Vegetables, and Cancer Risk

Clinical Oncology Alert

2010 Reader Survey

In an effort ensure *Clinical Oncology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The results will be used to ensure you are getting the information most important to you.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 1, 2010.**

In future issues of *Clinical Oncology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. appropriate treatment regimens	O A	O B	O C
2. quality-of-life treatments	O A	O B	O C
3. management of clinical symptoms	O A	O B	O C
4. uninsured patients	O A	O B	O C
5. new drug development	O A	O B	O C
6. breast cancer	O A	O B	O C
7. lung cancer	O A	O B	O C
8. prostate cancer	O A	O B	O C
9. cervical cancer	O A	O B	O C
10. FDA regulations	O A	O B	O C

11. What other topics would you like to see discussed in *Clinical Oncology Alert*? _____

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12. Are the articles in *Clinical Oncology Alert* newsletter written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

13. What type of information not currently provided in *Clinical Oncology Alert* would you like to see added?

Please rate your level of satisfaction with the the items listed:

	A. excellent	B. good	C. fair	D. poor
14. monthly case study	O A	O B	O C	O D
15. Rapid Review	O A	O B	O C	O D
16. the new look of *COA*	O A	O B	O C	O D
17. quality of newsletter	O A	O B	O C	O D
18. article selections	O A	O B	O C	O D
19. timeliness	O A	O B	O C	O D
20. quality of commentary	O A	O B	O C	O D
21. clearness of abstracts	O A	O B	O C	O D
22. overall value	O A	O B	O C	O D
23. customer service	O A	O B	O C	O D

24. Please describe your work place:

○ A. private practice ○ B. hospital ○ C. government institution ○ D. research

○ E. Other_____

25. Do you benefit from having important points highlighted in the articles? ○ A. Yes ○ B. No

26. To which other publications or information sources about oncology do you subscribe?

_____

_____

27. Which publication or information source do you find most useful, and why? _____

_____

28. Please list the top three challenges you face in your job today.

_____

_____

_____

29. What do you like most about *Clinical Oncology Alert*?

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30. What do you like least about *Clinical Oncology Alert* newsletter?

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31. Has reading *Clinical Oncology Alert* changed your clinical practice? If yes, how? _____

_____

Contact information_____

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Health Care Reform Update

What Health Care Reform Means to You A supplement to *Clinical Oncology Alert*

Increased provider access tops list of what clinicians will like about HC bill

Changes will take a few years

HEALTH CARE CLINICIANS AND ORGANIZATIONS LIKELY will find that the new health care reform bill's positive features outweigh its drawbacks, experts say.

The Patient Protection and Affordable Health Care Act, signed into law on March 23, 2010, by President Barack Obama, provides a series of changes to take place to health care insurance coverage, Medicare, Medicaid, prescription drugs, quality improvement initiatives, medical malpractice, and other items. These are to be implemented from 2010 to 2014.

"The thing that is so big is the coverage for tens of millions of people who don't have health insurance now," says **Cecil Wilson**, MD, an internist in Winter Park, FL, and the president-elect of the American Medical Association in Chicago, IL.

People no longer will have to worry about losing health care coverage for existing diseases if they lose their jobs, and increasing numbers of people will have access to preventive care, primary care, and disease management, Wilson adds.

"Those are the big things that make this such a sea change in my opinion," he says. "For physicians, this is good because they won't have to worry about their patients' insurance being cut off, and thus putting their patients at risk."

Hospitals will find that significantly more patients will have health care coverage, resulting in a decline in uncompensated care, says **Caroline Steinberg**, vice president for trends analysis for the American Hospital Association in Washington, DC.

"We also would expect that demand for care from formerly uninsured patients will increase," Steinberg says. "Hopefully, we'll see some increases in primary care so by the time they hit the hospital they won't have some of the same kinds of problems they've had before."

The new bill provides billions of dollars in funding for clinics that provide primary care to uninsured, indigent, and immigrant patients. In 2014, it also expands Medicaid to all non-Medicare eligible individuals who have incomes up to 133% of the federal poverty level. These initiatives could help send more people to primary care services and keep them from using the emergency room for non-emergency care, Steinberg adds.

"We may [identify] more people with conditions that require specialty care because once people have access to coverage they tend to use more health care across all levels of the system," Steinberg says. "So that could go either way."

Plus, hospitals should expect the next few years to continue to be rough fiscally since most of the more significant provisions in the bill will not be fully implemented until 2014.

"Our hospitals are telling us that uncompensated care is going up because of job losses and loss of insurance, and these people show up in hospitals," Steinberg says.

There won't be much improvement in the immediate future until the economy recovers and the government provides more funding for Medicaid, she notes.

More oncology patients will have access to care, as a result of the bill's prohibition of lifetime limits on the dollar value of coverage, which begins Jan. 1, 2014. There is a temporary national high-risk pool to provide health care coverage to people with pre-existing medical conditions, which will be in place between June 2010 and 2014.

"Many cancer patients who need repeated courses of treatment can easily exceed their caps and find themselves unable to afford needed treatment and medication," says **Allen S. Lichter**, MD, chief executive officer of the American Society of Clinical Oncology (ASCO), in a statement issued after the bill was signed.

By this fall, insurers will not be able to exclude children with pre-existing conditions from being covered by their family policy, and this also is a positive move, Lichter says.

The bill's focus on prevention and wellness will benefit infectious disease and public health initiatives.

"There are a few things in the bill that we're pleased to see stay in the final version," says **Michael Ochs**, government relations associate with the Infectious Diseases Society of America (IDSA) in Arlington, VA.

The bill's emphasis on wellness and disease prevention with billions of additional federal dollars for these is one example, Ochs says.

The bill's impact on physician and other provider payments is a more mixed bag, however. *(See story on*

physician payments, below.)

"There's a 10% incentive pay for primary care and general surgery," says **Jason A. Scull**, program officer for clinical affairs at IDSA.

"They're focusing on primary care in a lot of these new innovative payment models, but I think primary care does need to be incentivized," Scull says.

But the drawback is that cognitive specialists, like infectious disease specialists, cardiologists, and neurologists, could be shortchanged as the pie is cut differently, but not expanded.

"There will be unintended consequences," Scull notes. "Already last year the Centers for Medicare & Medicaid Services eliminated payments for consultation codes that cognitive specialties use to give them money to distribute elsewhere in the fee schedule and to send more to primary care physicians."

This redistribution of payments might result in fewer medical students choosing to spend extra years of training beyond their general internal medicine residency, he adds.

While the sweeping health care reform provides some specifics on how changes will occur in the industry, no one knows precisely how things will change until the regulatory details emerge, the experts say.

"There are a lot of moving pieces to this," Scull says. "I think it's anybody's guess to where all of this ends up." ■

Doctors will be more closely scrutinized with bill's provisions

Experts talk about bill's negatives

PAY ATTENTION TO THE NEW HEALTH CARE BILL'S REGulatory details, experts warn providers.

There are some items in the sweeping legislation that could result in more documentation, work, and risk for physicians and other providers.

For instance, the new bill makes it clear that the government wants doctors to be doctors and not own hospitals, says **LaDale K. George**, JD, a partner with Neal, Gerber, Eisenberg in Chicago, IL.

The bill puts a moratorium on any physician-owned hospitals in non-rural settings that were not Medicare providers as of December 2010.

"The new law says that the practice of physicians owning hospitals no longer is allowed," he explains. "If a physician owns or has a financial interest in a hospital and refers patients to that hospital, then every service the patient receives at the hospital is a Stark violation of $25,000 per incident."

Also, the anti-kickback law has been changed by the new bill.

"The way the new act changes it is that it appears to eliminate the need to have actual knowledge or specific intent to violate the statute," George says. "It moves in the direction of where the Stark law is where if you do not meet the safe harbors in which providers can refer to one another and engage in commercial practices together then you will be viewed as being guilty."

From physicians' perspectives, some of the other requirements will be more onerous, particularly as far as documentation and accounting are concerned.

For instance, the bill's Physician Payment Sunshine Provision requires physicians to disclose every payment they receive from pharmaceutical and biotech companies in excess of $100, and this includes drug samples. This could prove to be an accounting problem for physician investigators and others.

This likely will be a headache to physicians, who will have to keep track of every sample they receive and every payment that flows through to them for research, George says.

The new health care bill also appears to give physicians incentives and/or penalties depending on their compliance with reporting data as part of the physician quality reporting initiative (PQRI), which was established with the 2006 Tax Relief and Health Care Act.

"What's clear is that Congress is moving into the direction of mandating physicians to participate in PQRI and also moving in the direction of mandating physician resource use reporting," says **Jason A. Scull**, program officer for clinical affairs at the Infectious Diseases Society of America.

"These are somehow merged into a value modifier that also will adjust payment based on the quality of care they provide," Scull says.

About one of six eligible physicians now makes the reports, and about half of these receive incentive payments, he adds. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

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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Statins and risk of developing diabetes

Source: Sattar N, et al. Statins and risk of incident diabetes. *Lancet* 2010;375: 735-742.

THERE IS LITTLE DISPUTE REGARDING THE beneficial reduction in CV events seen with statin treatment of dyslipidemic patients. At the same time, however, conflicting evidence has suggested that statin treatment might be associated with an increased risk of new-onset diabetes.

Sattar et al performed a meta-analysis of data from large statin clinical trials (n = 13), totalling almost 100,000 patients. During a mean follow-up of 4 years, 9% more individuals developed new diabetes on a statin than patients not treated with a statin. Since CV risk reduction was still favorably influenced by statin treatment, this small increase incidence of diabetes was either not sufficient to offset other beneficial vascular effects, or, once diabetes developed, statin protection was already on board, or perhaps both factors were influential.

You may recall that in hypertension treatment trials, a similar problem has been identified. Chlorthalidone (ALLHAT) had a significantly greater risk for incidence of new diabetes than comparators, yet this adverse effect did not seem to adversely affect CV event rates.

The mechanism by which statins increase risk for diabetes is obscure. This data analysis calculated that 255 subjects would have to be treated with a statin for 4 years to incur 1 additional new case of diabetes. Fortunately, if the small increase is real, it is strongly counterbalanced by well-documented reductions in CV events.

Maximize benefits of metform in DM2

Source: Brown JB, et al. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* 2010;33:501-506.

TO DATE, CONTROLLED TRIALS INDICATE THAT no matter what pharmacotherapy is used to control glucose in type 2 diabetes (DM2), one can anticpate a progressive loss of control over time. Loss of efficacy is termed secondary failure: An initially effective medication later becomes insufficient to maintain control. It seems to me that this is too harsh an indictment of pharmacotherapy, since even if the medication continues with similar action over long time periods, confounders such as weight gain, inherent disease progression, and addition of confounding comorbidities might make it appear as if the medication is failing, when in reality, counterbalancing forces are increasing.

In any case, Brown et al performed an observational cohort study of DM2 subjects (n = 1799) initially treated with metformin monotherapy successfully (i.e., able to maintain an A1c < 7.0 without adding a second agent). Secondary failure was defined as either the addition of a second agent, or an increase of A1c above 7.0 while still on monotherapy. Subjects who required additional therapy within the first 6 months of metformin treatment were regarded as primary failure, and were excluded from this analysis.

In subjects able to maintain good control with initial metformin monotherapy, secondary failure occurred at a rate of 17% per year. Predictors of higher failure rates included longer duration of diabetes before treatment and higher baseline A1c at initiation of treatment. These data suggest that early initiation of treatment, especially when A1c is not yet markedly elevated, results in greater durability of metformin efficacy.

Prediabetes therapy and beta-cell function

Source: Hanley AJ, et al. Effect of rosiglitazone and ramipril on {beta}-cell function in people with impaired glucose tolerance or impaired fasting glucose. *Diabetes Care* 2010;33:608-613.

PREDIABETES (PDM) IS DEFINED AS EITHER impaired fasting glucose (FBG = 100-125 mg/dL), impaired glucose tolerance (IGT; 2-hour post-load glucose = 140-199 mg/dL), or supranormal but not diabetic A1c (A1c = 5.7-6.4). Untreated pDM predictably progresses to frank DM at a rate of about 7%-10% per year. Numerous interventions have been shown to alter the progression from pDM to diabetes, including diet, exercise, metformin, acarbose, orlistat, and thiazolidinediones; this year, nateglinide, an insulin secretagogue, was not confirmed to delay progression from pDM to diabetes.

Hopefully, treatments to prevent diabetes will also impact beta-cell function favorably, rather than simply compensate for progressive metabolic decline. The DREAM trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) randomized 5269 pDM subjects to ramipril and/or rosigliatoze. A substudy of DREAM (n = 982) had measurements of beta-cell function at baseline and periodically during the 3-year (median) follow-up, as well as measurements of progression from pDM to DM.

Subjects randomized to ramipril did not experience any meaningful change

in beta-cell function. In contrast, rosiglitazone-treated subjects enjoyed substantial improvements in beta-cell function. Benefits were less in pDM subjects who only manifest IFG compared with IGT or both.

In addition to reducing beta cells induced by glucotoxicity, thiazolidinediones lower free fatty acid levels, which may favorably affect beta-cell apoptosis.

Onychomycosis: Long-term follow-up

Source: Piraccini BM, et al. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol* 2010;62:411-414.

Although onychomycosis (ONCM) is often considered a cosmetic problem, some patients suffer significant disability due to foot pain, and difficulty wearing shoes. The treatment course for toenail ONCM is lengthy and costly. There are few data on long-term follow-up to ascertain recurrence rates, although prevailing opinion suggests recurrence is common.

Praccini et al performed a prospective study of ONCM patients (n = 73) who had been treated with pulse therapy (treatment 1 week/month for 6 months) with terbinafine or itraconazole. After clinical cure, subjects were prospectively followed for 7 years. Cure was defined as normalized clinical appearance and negative fungus culture.

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Patients were seen every 6 months during follow-up. Overall, recurrence developed in 16.4% of subjects. Each case of recurrence involved the same organism identified in the original infection. However, the recurrence rate for itraconazole was 3-fold greater than terbinafine. Terbinafine is widely regarded as the treatment of choice for toenail ONCM; this trial suggests superior durability of cure for terbinafine when compared with itraconazole.

Diagnostic yield of elective coronary angiography

Source: Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-895.

Current recommendations suggest that in stable persons under consideration for CAD evaluation, low-risk individuals be observed, high-risk patients be triaged to coronary angiography, and intermediate-risk persons be further stratified by means of non-invasive testing. Such guidance is structured to minimize unnecessary invasive investigations in low-risk individuals, and to identify — in the group of intermediate risk — those who merit follow-up with angiography.

The American College of Cardiology National Cardiovascular Data Registry provided information on patients without known CAD (n = 398,978) who received coronary angiography (electively) at hospitals in the United States during a 4-year interval commencing January, 2004.

Obstructive CAD was defined as at least 50% stenosis of the left main coronary artery (or greater degrees of stenosis of epicardial vessels). Catheterization determined that slightly more than one-third of patients had obstructive CAD. In addition to the disappointingly low percentage of individuals identified with CAD on angiography, this study also provided insights about the concordance of risk and use of non-invasive testing (i.e., stress testing). When non-invasive testing had preceded angiography, subjects' baseline risk category was at odds with the current recommendations focusing upon refinement of risk in persons at intermediate Framingham scores, in that those with high Framingham risk scores were disproportionately represented. The authors suggest that the diagnostic yield based upon current practice needs improvement.

Thyroid hormone analogue for dyslipidemia

Source: Ladenson PW, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010;362:906-916.

The role of statins in treatment of dyslipidemia is well established. There are, however, limitations of statins: Residual risk is substantial, not all persons can tolerate statins, and, even with full-dose statin treatment, some patients do not achieve lipid goals.

The role of the thyroid in lipid metabolism has long been a matter of scientific interest. It is recommended that patients with dyslipidemia undergo thyroid function testing since hypothyroidism, although only present in a small percentage of dyslipidemic patients, is readily correctible and offers meaningful lipid improvements. Enhancement of thyroid activity has favorable lipid effects. As far back as the 1960s, investigators were curious enough about thyroid hormone and vascular disease to enroll men in the Coronary Drug Project (1965) and randomize them to d-thyroxine, which was felt at the time (mistakenly) to have essentially no effect on sympathetic nervous system sensitivity, but favorable effects on lipids.

Eprotirome (EPR) is an analogue of thyroid homone which has preferential affinity for thyroid receptors that modulate lipid lowering, as compared to cardiac receptors. A randomized placebo-controlled, double-blind study was done among patients on an NCEP step 1 diet and a statin (simvastatin or atorvastatin). Patients (n = 329) received statin plus either EPR or placebo for 12 weeks.

At the end of the trial, very favorable lipid effects were reported with the addition of EPR to a statin: a 22%-32% reduction in LDL, a 6- to 9-fold increase in patients achieving an LDL < 100 mg/dL, as well as favorable effects on triglycerides and apoB (all dose-dependent). A small reduction in HDL was seen. There was no change in heart rate or BP. Selective activation of thyroid receptors may one day provide an additional path for successful lipid modulation.

PHARMACOLOGY WATCH

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

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.