# Update in Hematology and Oncology: Evidence Published in 2013

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Doing more with less in medical practice is a prescription not unfamiliar to most of today's practitioners. The "Choosing Wisely" initiative of the American Board of Internal Medicine Foundation aims to help accomplish this by reducing waste in the U.S. health care system. One initiative involves asking medical specialty societies to develop a list of 5 commonly used tests, treatments, or services that require reevaluation by patients and practitioners regarding their use (1). During the past year, both the American Society of Hematology and the American Society of Clinical Oncology have published their "Choosing Wisely" targets (2, 3). Of note, both societies' lists have in common reducing the use of certain types of surveillance imaging in asymptomatic patients after treatment with curative intent unless there is clear evidence of benefit in this setting.

The 12 articles summarized here represent a cross-section of important articles published in 2013 on both novel and existing therapeutics. Although there were certainly interesting reports of novel therapeutics in both hematology and oncology during the past year, many of the most important and widely read papers are indeed in keeping with the principle of reducing unnecessary or unproven interventions. In hematology, these included the publication of a randomized trial extending the applicability of limited red blood cell transfusion. Among the oncology reports, these included a publication of a randomized trial demonstrating no benefit from daily parenteral hydration in hospice patients. Although perhaps not inherently as exciting to some as reports on the efficacy of new therapeutics, such studies provide essential information for the practice of value-based patient care.

## Hematology

### A Restrictive Transfusion Strategy Improves Outcomes in Acute Upper Gastrointestinal Bleeding

**Villanueva C, Colomo A, Bosch A, et al.** Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21. [PMID: 23281973]

**Background:** The red blood cell transfusion threshold for critically ill hospitalized patients in the United States had traditionally been about 9 g/dL. This value was set by clinical practice at various institutions rather than driven by data. Large well-controlled randomized trials, supported by smaller clinical trials and observational studies, subsequently showed that a transfusion threshold of 7 g/dL was at least as effective and possibly safer in critically ill adults (4, 5). However, these studies generally excluded patients with ongoing blood loss as evidenced by a decrease in hemoglobin concentration or need for blood transfusion.

**Findings:** This trial randomly assigned 921 patients with acute upper gastrointestinal bleeding, as evidenced by hematemesis or melena, to a restrictive transfusion strategy (hemoglobin <7 g/dL) or a liberal transfusion strategy (hemoglobin <9 g/dL). Randomization was stratified by the presence or absence of cirrhosis. More patients in the restrictive group went without transfusion than those in the liberal group (225 of 461 [51%] vs. 61 of 460 [14%]; $P < 0.001$). Of note, the probability of survival at 6 weeks was higher with the restrictive strategy than with the liberal one: 95% versus 91% (hazard ratio for death with the restrictive strategy, 0.55 [95% CI, 0.33 to 0.92]; $P = 0.02$). In addition, the restrictive strategy group had statistically significant lower rates of rebleeding and lower rates of adverse events.

**Cautions:** Patients with massive bleeding were excluded from this trial, and patients with lower gastrointestinal bleeding were not studied, so the findings cannot be formally applied to these groups. In addition, as indicated by the data presented, the greatest survival benefit demonstrated with the restrictive transfusion strategy in this trial was primarily in individuals with Child–Pugh class A or B cirrhosis; no benefit was seen in Child–Pugh class C cirrhosis.

**Implications:** Given outcomes that are noninferior or even superior in a variety of clinical settings, restrictive transfusion strategies should be implemented for most critically ill patients. The current study extends findings previously reported in critically ill patients, including those with prior myocardial infarction and those with upper gastrointestinal bleeding. Even in the absence of a survival benefit, this strategy is associated with fewer complications, as well as reduction in the use of a valuable resource.

### Continued Anticoagulation With Warfarin During Pacemaker or Defibrillator Surgery Is Associated With Fewer Bleeding Complications

**Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators.** Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med. 2013;368:2084-93. [PMID: 23659733]

**Background:** Patients requiring placement of a pacemaker or implantable cardioverter-defibrillator (ICD) are often

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taking warfarin. Current guidelines for this situation recommend that patients at moderate to high risk for thromboembolic events, defined as a risk of at least 5% per year, discontinue warfarin and receive bridging therapy with heparin or low-molecular-weight therapy around the time of surgery (6). However, this strategy is associated with a notable incidence of device-pocket hematomas that necessitate further management, such as drainage, along with an overall increased utilization of medical resources.

**Findings:** A total of 681 patients requiring pacemaker or ICD placement were randomly assigned to discontinuation of warfarin 5 days before the procedure and heparin bridging or to continued warfarin without interruption. The median international normalized ratio on the day of surgery was 1.2 in the heparin-bridging group and 2.3 in the continued warfarin group. Major complications were uncommon in both groups. However, 54 of 338 patients (16%) in the heparin-bridging group developed clinically significant device-pocket hematomas versus 12 of 343 patients (3.5%) in the continued warfarin group (relative risk, 0.19 [CI, 0.10 to 0.36]; $P < 0.001$).

**Cautions:** The study was performed at 17 centers in Canada and 1 in Brazil, which raises the possibility that outcomes with this approach could differ in regions differing in the concomitant use of antiplatelet agents and other medications; however, this seems unlikely. This strategy of continued anticoagulation cannot be applied to the newer oral anticoagulant agents—dabigatran, rivaroxaban, and apixaban—until clinical trials with those agents are conducted.

**Implications:** Continuation of anticoagulation with warfarin maintained in the therapeutic range during pacemaker and defibrillator surgery appears to be safe and associated with fewer complications compared with interrupting therapy and bridging with heparin or low-molecular-weight heparin. This randomized trial may lead to additional randomized, controlled trials to augment smaller studies that have examined continued anticoagulation in the setting of other minor procedures, such as colonoscopy with biopsy and joint injections. Because in aggregate many thousands of such procedures are performed each year, there is the potential to improve care while reducing cost.

### Limiting D-Dimer Testing to Patients With Low or Moderate Pretest Probability of First Episode of Deep Venous Thrombosis Reduces Number of Tests

**Linkins LA, Bates SM, Lang E, et al.** Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. Ann Intern Med. 2013;158:93-100. [PMID: 23318311]

**Background:** Evaluation for the possibility of a first deep venous thrombosis (DVT) is a common clinical scenario. Reduction in unnecessary testing is desirable for the efficient diagnosis of this condition and to reduce cost. Previous studies have suggested that a combination of low pretest clinical probability and negative results on D-dimer testing can be used to identify patients who do not require further evaluation with ultrasonography (7). Application of this algorithm, however, still leads to ultrasonography in patients with low clinical pretest probability and modestly elevated D-dimer levels.

**Findings:** A total of 1723 patients were randomly assigned to a uniform testing strategy ($n = 863$) or to a selective testing strategy ($n = 860$). In the uniform testing strategy, all patients underwent D-dimer testing and those with a positive test result (defined as $\geq 0.5$ $\mu$g/mL) underwent ultrasonography. In the selective testing strategy, patients with low and moderate clinical pretest probability underwent D-dimer assay, whereas patients with high pretest probability went directly to ultrasonography. A positive test result requiring further evaluation was defined as 1 $\mu$g/mL or greater for patients with low clinical pretest probability and 0.5 $\mu$g/mL or greater for those with moderate clinical pretest probability. The incidence of symptomatic DVT at 3 months was the same in the 2 groups. However, the selective testing strategy was associated with a 21.8% (CI, 19.1% to 24.8%) reduction in D-dimer testing and a 7.6% (CI, 2.9% to 12.2%) reduction in ultrasonography.

**Cautions:** D-Dimer testing is not standardized, and the cutoff values used for this study may not be the same for different assays. In addition, issues with the use of D-dimer testing in inpatients led to lower-than-expected enrollment of this group, so the results apply only to outpatients.

**Implications:** Use of selective D-dimer testing with different thresholds to define a positive result in patients with low and moderate clinical pretest probability, along with moving directly to ultrasonography in patients with high clinical pretest probability, can reduce the number of unnecessary D-dimer and ultrasonography tests performed in outpatients undergoing evaluation for a first DVT episode.

### After Initial Course of Low-Molecular-Weight Heparin, Aspirin Is Effective for Thromboprophylaxis in Hip Surgery

**Anderson DR, Dunbar MJ, Bohm ER, et al.** Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med. 2013;158:800-6. [PMID: 23732713]

**Background:** Over the years, several different classes of anticoagulants have been used to reduce the incidence of venous thromboembolism (VTE) after hip replacement surgery. Several studies, including a very large clinical trial, showed that aspirin, an antiplatelet agent, decreased the incidence of pulmonary embolism and DVT in this setting (8). Although not compared directly, the superiority of anticoagulants over this antiplatelet agent has been assumed. These other agents, however, have been associated with a higher risk for bleeding and increased cost.

**Findings:** After 10 days of open-label dalteparin, 5000 U/d given subcutaneously, this double-blind, placebo-

controlled trial randomly assigned patients to continue receiving dalteparin ($n = 400$) or to receive aspirin, 81 mg/d ($n = 386$), for an additional 28 days. The study end point was symptomatic VTE. Continuation of aspirin therapy was noninferior to continuation of dalteparin therapy ($P < 0.001$, with noninferiority based on a minimum clinically important difference of 2.0%). However, the number of events was small in both the dalteparin (1.3%) and aspirin (0.3%) groups. Bleeding events did not significantly differ.

**Cautions:** This trial was stopped prematurely because of difficulty enrolling enough patients. In contrast to most trials of newer anticoagulants that evaluated all patients for asymptomatic DVT by using ultrasonography, this trial evaluated only symptomatic patients. In addition, some newer anticoagulants appear to have greater efficacy than low-molecular-weight heparin in this setting.

**Implications:** Although this study had limitations, it raises the question of whether the administration of other prophylactic agents, such as fondaparinux or rivaroxaban, for a limited duration of 10 days, followed by aspirin, would produce results similar to those in this study. Shorter treatment with dalteparin (or a similar agent) followed by aspirin as implemented in this trial could reduce the complexity of administration and cost associated with thromboprophylaxis after hip surgery.

### Intermittent Pneumatic Compression Reduces Risk for DVT in Patients With Stroke

**Dennis M, Sandercock P, Reid J, et al; CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration.** Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet. 2013;382:516-24. [PMID: 23727163]

**Background:** The prevention of DVT in patients who have just had a stroke and are immobile represents a challenging clinical scenario. Concerns for hemorrhagic complications often preclude use of parenteral anticoagulants, such as low-molecular-weight heparin. Graduated compression stockings do not appear to be effective in this setting, and there was previously a paucity of data on use of intermittent pneumatic compression (IPC) in patients who had had a stroke, despite the documented efficacy of this prophylactic measure in the surgical setting (9).

**Findings:** In this trial, 2876 immobile patients who had had a stroke (mean age, 76 years) were randomly assigned to IPC ($n = 1438$) or no IPC ($n = 1438$). The primary outcome, of proximal vein DVT on screening compression duplex ultrasonography, was seen in 8.5% of patients treated with IPC versus 12.1% of patients not treated with IPC, for an absolute risk reduction of 3.6 percentage points (CI, 1.4 to 5.8 percentage points). After exclusion of patients who could not be evaluated according to the protocol, the odds ratio was 0.65 (CI, 0.51 to 0.84; $P = 0.001$). There was a trend toward improved survival in the IPC group ($P = 0.057$). The only notable potential adverse effect of IPC was skin breaks, which occurred in 3.1% of the IPC group and 1.4% of the non-IPC group ($P = 0.02$).

**Cautions:** This trial was not blinded, so there could have been bias in the assessors' performing ultrasonography. In addition, adherence to IPC was only moderate. However, if anything, this might have led to underestimation of the effect size.

**Implications:** Intermittent pneumatic compression appears to be a safe and effective strategy for the reduction of DVT in immobile patients who have had a stroke. Because IPC can be used in patients with both ischemic and hemorrhagic infarcts without concern for bleeding, it should be of clinical utility, particularly since it may be associated with a survival benefit.

### Apixaban Is Effective Treatment for VTE

**Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators.** Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808. [PMID: 23808982]

**Background:** During the past few years, the U.S. Food and Drug Administration has approved several new oral anticoagulants for different indications, including rivaroxaban, a factor Xa inhibitor also indicated for the treatment of VTE (10). Apixaban is another oral factor Xa inhibitor administered in fixed doses twice daily. It is a substrate of both CYP3A4 and permeability glycoprotein, and it is metabolized mainly by CYP3A4 with minor contributions from other cytochrome enzymes. This results in important drug interactions, including those with ketoconazole and rifampin. Currently, no antidote is available for this agent.

**Findings:** This double-blind trial randomly assigned 2691 patients to apixaban, 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months, and 2704 to enoxaparin transitioned to warfarin for 6 months. The primary efficacy end point of recurrent symptomatic VTE or death related to VTE occurred in 59 (2.3%) of those receiving apixaban and 71 (2.7%) of those receiving enoxaparin–warfarin. This met the predefined boundary for noninferiority ($P < 0.001$). Major bleeding outcomes were significantly lower with apixaban (0.6%) than with enoxaparin–warfarin (1.8%), and this was mirrored in the outcomes for minor bleeding (4.3% vs. 9.7%) ($P < 0.001$ for both comparisons).

**Cautions:** Patients receiving aspirin dosages greater than 165 mg daily, as well as individuals with creatinine values of 221 $\mu$mol/L (2.5 mg/dL) or more, were excluded from this trial, so the safe use of apixaban in these populations cannot be inferred from the current trial. Because of the agent's metabolism and partial renal elimination, clinicians must consider drug–drug interactions and renal function when prescribing apixaban.

**Implications:** Although not yet approved by the U.S. Food and Drug Administration for the treatment of VTE, apixaban may eventually provide another option for oral management of this complication. Use of these new oral anticoagulants may further transition the treatment of VTE into the outpatient setting. In addition, the relative ease of use and the safety profile demonstrated in clinical trials conducted with these agents may increase the overall number of candidates for long-term anticoagulation. A report on the safety and efficacy of apixaban for extended-duration anticoagulation has already been published (11).

## Oncology

### R-CHOP Given Every 21 Days Remains Standard of Care in First-Line Treatment of Diffuse Large B-Cell Non-Hodgkin Lymphoma

**Cunningham D, Hawkes EA, Jack A, et al.** Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013;381:1817-26. [PMID: 23615461]

**Background:** Rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) given in 21-day cycles represents a standard of care in the management of diffuse large B-cell non-Hodgkin lymphoma (12). Efforts to improve upon this regimen by using alternative or additional agents have generally not demonstrated greater efficacy when evaluated in large randomized, controlled trials. Because treatment delays have been associated with adverse outcomes, a question that remains is whether increased treatment intensity facilitated by use of growth factors can improve efficacy.

**Findings:** In this trial, R-CHOP-21 consisted of standard doses of this regimen administered every 21 days for a total of 8 cycles, with growth factor support at the discretion of the investigator; R-CHOP-14 consisted of a very similar regimen administered for 6 cycles every 14 days, followed by 2 further rituximab infusions every 2 weeks with growth factor support on days 4 to 12 of each chemotherapy cycle. A total of 1080 patients were equally randomly assigned between the 2 groups. Overall and 2-year progression-free survival did not differ between the treatment groups, and subset analysis did not indicate that any subset of patients benefited from the R-CHOP-14 regimen. Although grade 3 or 4 neutropenia was more frequent with R-CHOP-21 without prophylactic growth factor use (60% vs. 31%), grade 3 or 4 thrombocytopenia was more common with R-CHOP-14 (9% vs. 5%).

**Cautions:** Although the outcome of the 2 groups was similar, this trial was powered to demonstrate superiority of the R-CHOP-14 regimen over the R-CHOP-21 regimen rather than noninferiority. Therefore, this trial cannot be used as the basis for justifying the treatment of diffuse large B-cell non-Hodgkin lymphoma with R-CHOP-14 as an alternative to R-CHOP-21.

**Implications:** R-CHOP-21 administered without prophylactic growth factor support remains the standard of care for patients with diffuse large B-cell non-Hodgkin lymphoma. Although some investigators postulated that certain high-risk subsets of patients might benefit from R-CHOP-14, this did not prove to be the case in this trial. Future trials may examine whether using combinations of newer immunotherapy agents with the CHOP regimen offers improvement.

### Treatment of High-Risk Smoldering Myeloma With Lenalidomide and Dexamethasone Improves Overall Survival

**Mateos MV, Hernández MT, Giraldo P, et al.** Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med. 2013;369:438-47. [PMID: 23902483]

**Background:** Smoldering, or asymptomatic, multiple myeloma is defined by an IgG or IgA monoclonal protein level in plasma of at least 3 g/dL or at least 10% clonal plasma cells in the bone marrow in the absence of hypercalcemia, renal insufficiency, anemia, or bone lesions. Traditionally, management of smoldering myeloma has consisted of close observation, followed by initiation of chemotherapy when symptoms develop (13). However, with the development of chemotherapy drugs demonstrating greater activity in multiple myeloma, the issue of potential benefit from earlier treatment has been revisited.

**Findings:** Patients with smoldering myeloma at high risk for progression to symptomatic disease, as evidenced by at least 95% aberrant plasma cells in the bone marrow along with reductions of at least 25% from normal values in 1 or 2 uninvolved immune globulins, were enrolled in this open-label trial; 119 individuals were randomly assigned to treatment ($n = 57$) or observation ($n = 62$). Treatment consisted of nine 4-week cycles of lenalidomide and dexamethasone, followed by a maintenance regimen of lenalidomide for 2 years. With a median follow-up of 40 months, both the median time to progression (time to progression not reached vs. 21 months; hazard ratio for progression, 0.18 [CI, 0.09 to 0.32]; $P < 0.001$) and the 3-year survival rate (94% vs. 80%; hazard ratio for death, 0.31 [CI, 0.10 to 0.91]; $P = 0.03$) were higher in the treatment group. Toxicity associated with treatment was generally modest.

**Cautions:** This relatively small trial evaluated patients with high-risk smoldering multiple myeloma that met specific criteria. Given the potential adverse events and expense associated with lenalidomide treatment, these findings should not be generalized to all patients with smoldering multiple myeloma. Additional trials to confirm and expand these findings will be helpful.

**Implications:** Patients with smoldering multiple myeloma and features indicating a high risk for progression appear to benefit from treatment with lenalidomide and dexamethasone followed by maintenance therapy with lenalidomide. Such treatment may be associated with improved survival because complications usually triggering treatment, such as renal failure, are avoided. A new treatment paradigm is therefore evolving, and suggestions for reclassifying a subset of patients with smoldering multiple myeloma as having active disease have already appeared in the literature (14).

### Maintenance Chemotherapy Benefits Patients With Advanced Nonsquamous Non–Small Cell Lung Cancer

**Paz-Ares LG, de Marinis F, Dediu M, et al.** PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013;31:2895-902. [PMID: 23835707]

**Background:** Non–small cell lung cancer (NSCLC) is estimated to have been responsible for about 160 000 deaths in the United States in 2013. Despite chemotherapy, locally advanced (stage IIIB) and metastatic (stage IV) disease has been associated with poor overall survival. The identification and application of several chemotherapy agents with activity in NSCLC, such as pemetrexed, a multitargeted antifolate agent, have resulted in modest improvement in survival. Because further improvement is highly desirable, the potential value of maintenance chemotherapy has been investigated. Although the primary end point of progression-free survival was previously reported from this trial (15), the trial was also powered to assess overall survival, a more relevant end point.

**Findings:** In the trial, 939 patients with advanced NSCLC received 4 cycles of pemetrexed–cisplatin induction chemotherapy. The 539 patients with no disease progression and good performance status (Eastern Cooperative Oncology Group performance status of 0 or 1) were randomly assigned 2:1 to maintenance pemetrexed or to placebo on day 1 of 21-day cycles. After 397 deaths and a median follow-up of 24.3 months for patients remaining alive, maintenance therapy was associated with a survival duration of 13.9 months versus 11.0 months for placebo (hazard ratio, 0.78 [CI, 0.64 to 0.96]; $P = 0.02$). All subgroups had a similar improvement in overall survival. Drug-related grade 3 and 4 adverse effects, including fatigue, anemia, and neutropenia, were more common in patients receiving pemetrexed.

**Cautions:** Some patients in the placebo group had prolonged periods without disease progression. Therefore, it is possible that further work may lead to methods to identify individuals who might best benefit from maintenance chemotherapy, rather than from therapy at disease progression. This would reduce the number of individuals experiencing the adverse events associated with continued treatment as well as potentially reduce the associated cost.

**Implications:** Use of maintenance chemotherapy in patients with advanced NSCLC was associated with an almost 3-month improvement in median survival that was associated with moderate adverse effects of treatment. This approach to treatment represents continued progress in the development of management options for advanced NSCLC, which has traditionally been associated with poor outcomes.

### In Advanced *ALK*-Positive Lung Cancer, Crizotinib Improves Progression-Free Survival, but Not Overall Survival, Compared With Chemotherapy

**Shaw AT, Kim DW, Nakagawa K, et al.** Crizotinib versus chemotherapy in advanced *ALK*-positive lung cancer. N Engl J Med. 2013; 368:2385-94. [PMID: 23724913]

**Background:** Rearrangements in the anaplastic lymphoma kinase (*ALK*) gene are found in about 5% of cases of NSCLC. This may seem like a small percentage; however, in a cancer that was diagnosed in about 228 000 individuals in the United States in 2013, it represents a substantial number of affected individuals. Crizotinib is an oral tyrosine kinase inhibitor that targets ALK, among others. In phase I and phase II trials, it produced objective response rates of about 60% in patients with advanced *ALK*-positive NSCLC, most of whom had received prior chemotherapy (16). How well treatment with crizotinib compared with conventional chemotherapy in the second-line treatment setting was unknown.

**Findings:** Individuals with locally advanced or metastatic *ALK*-positive NSCLC who had received at least 1 previous platinum-containing chemotherapy regimen were randomly assigned to treatment with oral crizotinib twice daily ($n = 173$) or to chemotherapy with intravenous pemetrexed or docetaxel every 3 weeks ($n = 174$). The rate of response to crizotinib was significantly higher than that for chemotherapy (65% vs. 20%). The primary end point of median duration of progression-free survival was 7.7 months with crizotinib and 3.0 months with chemotherapy (hazard ratio for progression or death with crizotinib, 0.49 [CI, 0.37 to 0.64]; $P < 0.001$). Crizotinib was also associated with greater improvement in quality of life than chemotherapy. However, an interim analysis of overall survival revealed no significant difference between crizotinib and chemotherapy.

**Cautions:** Although crizotinib was not associated with an apparent overall survival benefit, this may have been because of crossover from chemotherapy to crizotinib that occurred during this trial. This phenomenon has previously been observed with trials of targeted therapies, such as imatinib, which have ultimately been demonstrated to have a beneficial effect on survival.

**Implications:** Crizotinib is an important therapeutic option for patients with *ALK*-positive NSCLC. In the

second-line setting for locally advanced and metastatic disease, it is associated with a better response rate and progression-free survival than is chemotherapy, and a beneficial effect on overall survival is not unlikely. Its use represents a new standard of care in the treatment of patients with *ALK*-positive NSCLC.

### Abiraterone Improves Radiographic Progression-Free Survival in Castration-Resistant Metastatic Prostate Cancer

**Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators.** Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138-48. [PMID: 23228172]

**Background:** Metastatic prostate cancer is typically first treated with hormonal manipulation. Once the cancer progresses, despite low testosterone levels, it is defined as castration resistant. Appropriate therapy for castration-resistant prostate cancer depends on patient preference and the clinical scenario. Second-line hormonal manipulation, potentially desirable because it may be associated with fewer adverse effects of treatment, has not been associated with a survival benefit (17). Abiraterone is an inhibitor of cytochrome P-450c17, which is needed for androgen synthesis. It was previously shown to be effective in improving overall survival after chemotherapy, but whether a similar survival benefit would occur in patients previously untreated with chemotherapy was not known.

**Findings:** This double-blind trial randomly assigned patients to abiraterone acetate and prednisone ($n = 546$) or to placebo and prednisone ($n = 542$). The median duration of radiographic progression-free survival was 16.5 months with abiraterone and prednisone versus 8.3 months with placebo and prednisone (hazard ratio for abiraterone and prednisone over placebo and prednisone, 0.53 [CI, 0.45 to 0.62]; $P < 0.001$). With a median follow-up of 22.2 months, the median overall survival with abiraterone and prednisone was not reached but was 27.2 months with placebo and prednisone; however, this did not cross the efficacy boundary. Abiraterone and prednisone showed superiority in several secondary end points, including opiate use for cancer-related pain and decline in performance status.

**Cautions:** The interpretation of overall survival, which was markedly prolonged in this trial even with placebo and prednisone in comparison with results of other trials, may be confounded by the use of prednisone, an active agent, in the comparator group, as well as by the variety of subsequent therapies used after disease progression during therapy.

**Implications:** Abiraterone represents an advance in the care of patients with castrate-resistant prostate cancer. It offers another therapeutic option to those who are asymptomatic or mildly symptomatic, among others. It may eventually replace the use of diethylstilbestrol and ketoconazole and displace other therapies, such as sipuleucel-T and docetaxel, in the treatment sequence.

### Hospice Patients Do Not Benefit From Receiving 1 L of Normal Saline Daily

**Bruera E, Hui D, Dalal S, et al.** Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. J Clin Oncol. 2013;31:111-8. [PMID: 23169523]

**Background:** The importance of palliative care in the overall management of patients with cancer is increasingly being recognized on the basis of emerging evidence (18). However, optimal strategies for many areas of this field remain to be defined. One controversial area is whether patients receiving end-of-life palliative care should receive parenteral hydration when they are unable to maintain adequate fluid intake. Such patients generally receive hydration in acute care facilities, which is then discontinued after transition to the hospice setting.

**Findings:** Patients at 6 hospices were randomly assigned to receive saline, 1 L (hydration) or 100 mL (placebo), daily over 4 hours. Dehydration symptoms, quality of life, and overall survival did not significantly differ between those treated with hydration ($n = 63$) and those receiving placebo ($n = 66$).

**Cautions:** It is possible that the frequent nursing visits and assessments provided to individuals in both study groups may have eclipsed any small benefit from hydration alone. In addition, because the study excluded patients with severe dehydration, as indicated by hypotension or altered mentation, the findings do not apply to these individuals.

**Implications:** Although relatively small, this trial does provide data that support not routinely providing intravenous hydration to hospice patients. The data may help providers explain this course of management to patients and family members, who are often concerned that withholding fluids may be associated with discomfort or hastened demise.

From the U.S. Food and Drug Administration, Silver Spring, Maryland.

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