Adapting Practice in the Face of New Data

By Christopher Stokoe, MD

A challenge that every oncologist must struggle with is keeping up with the rapidly changing science that defines our specialty. New therapeutics, new indications for old therapeutics, diagnostics, treatment criteria, guidelines, and so on besiege us daily. Often, the science that underpins this revolution is based on molecular pathways that have been defined since we were in fellowship.

Making sense of this voluminous amount of data requires considerable effort. Add to the scientific revolution the demands of keeping up with changes in government and insurance regulations, and it is easy to understand that oncologists are hard pressed to adapt.

How do oncologists adapt their practice patterns in the face of a bombardment of new information? What influences us to make changes to current treatment regimens? Do we change our practice patterns as soon as new information is available, or at a later time? I see several scenarios that affect change in my practice. It is easy to adapt to change in the setting of a new therapeutic for a disease in which no effective therapy exists. It is easy to adapt to a change in treatments when data are clear and overwhelming. More difficult are the scenarios where data are less clear or where changes are forced by changing reimbursement. This article examines examples of each of these scenarios, and offers my reflections as an individual oncologist on change.

Until recently, a rare form of hemolysis, paroxysmal nocturnal hemoglobinuria (PNH), had no disease-specific treatment. Patients were treated symptomatically with steroids and transfusions, which did little to affect the underlying condition. In March 2007, the FDA approved the monoclonal antibody eculizumab for the treatment of PNH.¹ Eculizumab binds to C5 and inhibits complement-induced intravascular hemolysis. For those PNH patients who require treatment, even with the significant financial cost of eculizumab, this drug will be used to treat an otherwise untreatable and devastating disease. It is unlikely physicians will say, "I need more data for this drug," if faced with the need to treat a PNH patient. Eculizumab is the only FDA-approved treatment for PNH, and the only drug proven to help with the consequences of PNH, including hemolysis and thrombosis.^{2,3} Adapting clinical practice to this data is easy—there are no other treatment options for PNH.

Another easy scenario is characterized by the overwhelming data that was presented supporting the use of trastuzumab (Herceptin; Genentech, South San Francisco, CA) in adjuvant breast cancer treatment. At ASCO's annual meeting in May 2005, three important trials regarding the use of adjuvant trastuzumab in early-stage breast cancer were presented. Two trials—NSABP B31 and N9831—were similar in design and eligibility and therefore were analyzed together.⁴ In these studies, more than 3,000 patients received chemotherapy with doxorubicin and cyclophosphamide for four cycles followed by paclitaxel (administered every 3 weeks for four cycles, or weekly for 12 treatments) after resection of their primary tumor. In the trastuzumab arm, patients received concurrent paclitaxel and trastuzumab, and the trastuzumab was continued to complete a total of 52 weeks of treatment. The results were impressive, with statistically significant improvements in both disease-free survival (DFS) and overall survival (OS). There was a 52% decrease in mortality and recurrence. In the HERA (HERceptin Adjuvant) trial from Europe, patients were randomly assigned to placebo or trastuzumab for 1 or 2 years after adjuvant chemotherapy.⁵ After 1 year of follow-up, improvement in DFS was significant, with a 46% decrease in mortality and relapse. The results of these trials were so significant that change in practice patterns occurred quickly. Oncologists are rarely presented with such impressive data for cancer treatment.

Adjusting practice patterns to adjuvant trastuzumab was made easier for several other reasons. Trastuzumab was not a new drug in oncology at the time of the 2005 ASCO Annual Meeting. Oncologists were experienced in using the drug on a regular basis for patients with advanced human epidermal growth factor receptor 2/*neu*-positive breast cancer.⁶ Apart from cardiac issues, trastuzumab is well tolerated, with relatively few adverse effects. Anecdotal evidence suggests some oncologists even used adjuvant trastuzumab in select patients before these data were available. This is an example of when data become available that changes the therapeutic indications of an existing drug; alterations in physician practice patterns are readily and more easily made.

More often we are presented with intriguing but difficult data. An example is data presented at the ASCO 2008 annual meeting by the Austrian Breast Cancer Group: the ASCSG-12 trial.⁷ These data suggest an alternative indication for an existing drug, zoledronic acid (Zometa; Novartis, East Hanover, NJ). Zoledronic acid is also well known to oncologists for its use in prostate and breast cancer patients with bone metastasis. In this four-arm trial, patients with stage I or II breast cancer underwent random assignment to either tamoxifen or anastrozole with or without zoledronic

acid. The primary end point of this trial was to look at DFS with secondary end points including recurrence-free survival (RFS) and OS. There was no difference with regard to DFS, RFS, and OS between tamoxifen and anastrozole. However, there was significant improvement in DFS and RFS in patients undergoing random assignment to receive zoledronic acid. Notably, data from the Zometa-Femara Adjuvant Synergy Trial presented at the San Antonio Breast Cancer Symposium 2008 confirmed a significant DFS benefit in patients with early-stage breast cancer who received zoledronic acid.⁸ These data show that a drug used in a supportive role for patients with stage IV breast cancer with bone metastasis has a benefit in decreasing the risk of recurrent disease (both local and distant) in patients with early-stage breast cancer. My guess is that on hearing these data, most oncologists did not return to their practice and incorporate zoledronic acid into their early-stage breast cancer adjuvant regimens. This would be in contrast to how, almost instantaneously, trastuzumab became part of regimens for patients with human epidermal growth factor receptor 2/*neu*-positive early breast cancer after release of its adjuvant data.

Why the difference, especially considering that the data for zoledronic acid seem convincing? One reason may be that there is no OS benefit, although there is statistically significant DFS and RFS. Oncologists may also be waiting for additional studies that will confirm the data of the ASCSG-12 trial to better understand the safety of zoledronic acid in this population. To change suddenly from using a drug in a supportive role in patients with advanced disease to a therapeutic role in patients who have early disease may be difficult for physicians. Another factor that must be considered is reimbursement. Many insurance companies question the use of zoledronic acid in patients without documented bone metastasis. Balancing all of these issues, oncologists may wait for their colleagues to change their treatment patterns before doing the same or wait until this treatment becomes part of accepted guidelines, such as National Comprehensive Cancer Network.

At times, data become available suggesting that what we are doing routinely in clinical practice may be harmful to our patients. Changes in practice are motivated by this knowledge, but also by the payors' recognition that they do not want to pay for a therapeutic that is inappropriate. A recent example is the issue with *KRAS* mutations in the treatment of colorectal cancer patients with epidermal growth factor receptor (EGFR) inhibitors. *KRAS* is an oncogene involved in intracellular signaling via the EGFR pathway. When mutated, *KRAS* results in continued cell proliferation along the EGFR pathway, and occurs even in the presence of an EGFR inhibitor. In April 2008, an article by Amado et al⁹ revealed that patients with mutations in the *KRAS* oncogene had no response to therapy with the EGFR inhibitor panitumumab (Vectibix; Amgen, Thousand Oaks, CA). EGFR inhibitors are routinely used in colorectal cancer

treatment alone or in combination without analysis of the *KRAS* mutation. During the 2008 annual meeting of ASCO, two additional studies (the CRYSTAL [Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer] trial and Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer [OPUS] trial) revealed no benefit to EGFR inhibitors in combination with chemotherapy for patients with mutations of *KRAS*, yet clear benefit in patients without a mutation. In the CRYSTAL trial, there was a trend towards shorter PFS in patients with *KRAS* mutations who received cetuximab (Erbix; ImClone Systems, Branchburg, NJ). The Capecitabine, Irinotecan, Oxaliplatin 2 [CAIRO2] study by the Dutch Colorectal Cancer Group combined bevacizumab (Avastin; Genentech) and cetuximab along with chemotherapy in first-line treatment for patients with metastatic colorectal cancer.¹⁰ Interestingly, there was no benefit with the combination of bevacizumab and cetuximab, even in wild-type *KRAS* patients. However, patients with *KRAS* mutations seemed to do worse with the addition of cetuximab. These trials suggest that administering an EGFR inhibitor in the setting of a *KRAS* mutation could be harmful to patients. These data are likely to be practice-changing for most oncologists. The suggestion that EGRF treatment may be harmful in *KRAS* mutation patients obliges physicians to perform a *KRAS* analysis and wait for the results before starting EGFR treatment in colorectal cancer patients. (Recognition of this fact led ASCO to release guidance to its members regarding *KRAS* testing—see the ASCO Provisional Clinical Opinion.¹¹)

Cost plays a significant role in the delivery of medical care. This is especially true of oncology, where chemotherapy and supportive drugs are often expensive. As a result, reimbursement for a given therapy is an important consideration that oncologists must take into account in the care of their patients. In all of the scenarios I have discussed, reimbursement policy has had an effect on the adoption of the therapy. Zoledronic acid seems to improve DFS in early-stage breast cancer, yet some insurance companies will not cover the expense at this time. Although these new data may result in a desire to change a practice pattern, it will not occur without insurance approval. This is not unique to US oncologists, as one recalls the difficulties oncologists faced in the United Kingdom with the trastuzumab data.¹²

Another example of reimbursement policy affecting practice is the Centers for Medicare and Medicaid Services guidelines with regard to erythropoietin-stimulating agents. The changes in coverage forced an abrupt change in how these drugs are administered to Medicare patients. The government based its guidelines on safety concerns, as data suggested adverse outcomes for cancer patients receiving erythropoietin-stimulating agents. Regardless of how an individual physician interprets the literature with regards to the safety of these drugs, it would be difficult to for an individual oncologist to

continue prescribe these expensive agents in the face of denial of payment.

Numerous factors are considered before making changes to a practice pattern. Cost, toxicity, real benefit over existing therapies, convenience, insurance approval, and other therapeutic options are just a few examples. It is rare to be provided with overwhelming impressive data, such as that with adjuvant trastuzumab. More often in oncology, the benefit of new treatment regimens over current standards is small, incremental, and nuanced. Therefore, when new data are presented, oncologists may wait before changing their practice patterns. These lessons have been reinforced over the years, seeing new treatment strategies' reported benefits fail the test of scrutiny—for example, bone marrow transplantation for high-risk breast cancer. Some oncologists may change their practice in 1 day on the basis of new data, whereas others may wait for a month, 6 months, or 1 year.

References

1. Dmytrijuk A, Robie-Suh K, Cohen MH, et al: FDA report: Eculizumab (Soliris) for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Oncologist* 13:993-1000, 2008
2. Brodsky R, Young N, Antonioli E, et al: Multicenter phase III study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood* 111:1840-1847, 2008
3. Hillmen P, Muus P, Dührsen U, et al: Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood* 110:4123-4128, 2007
4. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 353:1673-1684, 2005
5. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 353:1659-1672, 2005
6. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001
7. Gnant M, Milneritsch B, Schipfinger W, et al: Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. *J Clin Oncol* 26:6S, 2008 (suppl 2; abstr LBA4)
8. Eidtmann H, Bundred NJ, DeBoer R, et al: The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36 months follow-up of ZO-FAST. *San Antonio Breast Cancer Symposium 2008* (abstr 44)
9. Amado RG, Wolf M, Peeters M, et al: Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 26:1626-1634, 2008
10. Punt CJA, Tol J, Rodenburg A, et al: Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). *J Clin Oncol* 26:180S, 2008 (suppl; abstr LBA4011)
11. Morton RF, Hammond EH: ASCO provisional clinical opinion: KRAS, cetuximab, and panitumumab—Clinical implications in colorectal cancer. *J Oncol Pract* 5:71-72, 2009
12. National Institute for Health and Clinical Excellence UK: <http://www.nice.org.uk/>

The comfort of an individual physician in changing practice on the basis of new data is perhaps the most important factor. Treatment habits are often tough to break, and oncologists must become comfortable with treatments and their associated adverse effects. Regardless of what motivates an individual oncologist to make a practice change, the explosion of new oncology data is forcing us to evaluate how we practice. Indeed, understanding how we adapt to changes in our science and the mechanics of our practice will have ramifications for our satisfaction with practice and potentially the health of our profession.

Christopher Stokoe, MD, is a medical oncologist in practice with Texas Oncology, Plano, TX. Contact him at christopher.stokoe@usoncology.com.

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