Personalized Cancer Care: A New Paradigm in Oncology

A look at real-world implementation issues

Personalized cancer care is an emerging strategy in medical oncology. The theme of the 2009 American Society of Clinical Oncology (ASCO) meeting—chosen by ASCO's then-president Richard Schilsky, MD, was personalized cancer care, highlighting the importance of this issue.[1] Bottom line: improved outcomes for patients—including better survival and higher clinical benefit rates—warrant individualization of therapy whenever possible. One national oncology blog (Medscape, September 2, 2009) emphasized that this new paradigm implies that oncologists should consider how implementation of personalized cancer care could impact the nature of their practice and relationships with their colleagues and referring physicians, as well as their staff and patients.

The lay press is also exhibiting an emerging awareness about personalized medicine.[2] Patients are beginning to come for cancer consultations with an expectation that their care will be personalized. Patients also expect that their physicians will implement all of the appropriate testing and treatment decisions to allow patients to access the most individualized treatment available. Indeed, many patients, disappointed in the discussion about personalized medical care, seek second opinions elsewhere, usually from academic medical centers.

Because of this emerging trend, physicians need to re-evaluate the way in which they care for cancer patients. Community cancer centers and oncology practices should optimally and appropriately incorporate all of the validated technologies of personalized cancer treatment advances so that their care is state-of-the-art, effectively meeting the needs of their patients. This article addresses several timely issues related to personalized cancer care, including:

- What opportunities for personalized cancer treatment exist at the present time?
- What new tools are available to help a community cancer center or oncology practice to personalize care for their patients and remain at the "front of the curve?"
- How does a community cancer center or oncology practice effectively implement personalized cancer care?

by Cary A. Presant, MD, FACP; Pat Whitworth, MD, FACS; Emery Salom, MD; Dirk Davidson, MD; Karl M. Rogers, MD; Swapnil Rajurkar, MD; and Allan Hallquist, MD

Defining Personalized Cancer Care

Personalized cancer care is more comprehensive than just a molecular test. Personalized cancer care encompasses several different aspects of evaluation, decision, and judgment that require a complex evaluation of the patient.

First, tumor characteristics must be evaluated to define the precise histology, stage, and genotype and/or phenotype of the neoplasm itself. This information is necessary to predict what therapeutic modalities might work best, and establish a prognosis that can influence treatment recommendations. This comprehensive evaluation can take place at the initial evaluation of the patient's tumor, prior to any therapy. It can also take place at a subsequent evaluation of the patient's tumor after recurrence or progression, since the characteristics of cancers often vary over time and treatment. For suggestions on how to personalize non-small cell lung cancer treatment see box at right.

Personalizing the Care of Non-small Cell Lung Cancer

To help in the decision-making process, physicians should answer such questions as:

- Prior to thoracotomy or bronchoscopy is fresh tissue needed for analyses (e.g., chemoresponse, gene target identification, mutation analysis)?
- Postoperatively, is pathology review or immunohistochemistry (IHC) needed to determine if this is definitively an adenocarcinoma?
- Should EGFR, K-RAS and B-RAF analyses be performed to determine mutations for erlotinib planning?
- If irinotecan is planned, should testing of UGT1A1*28 polymorphisms be performed to adjust dosing?

The next component is an evaluation of the patient with regard to the presence of and severity of comorbidities and reductions in organ function that may individualize the patient's need for or tolerance of different treatments (e.g, renal, liver, cardiac, and pulmonary function). Molecular polymorphisms that can predict the pharmacological disposition of drugs should also be studied.

Following an evaluation of the neoplasm and the patient, physicians must communicate effectively with the patient and family about all available treatment options, the expected treatment toxicities, and the possible necessity for subsequent additional evaluations (even additional biopsies) to update the treatment plan. This discussion is a comprehensive visit and requires a close relationship between the physician, the patient, and the patient's family or advocate. Once the patient understands the ramifications of the individualized treatment, he or she must decide to consent to the treatment or modify the recommendations.

Next, physicians must document the comprehensive personalized treatment plan (together with the rationale for the decisions) and, if necessary, obtain authorization from the payer or health plan. Having a standardized form for this treatment plan—such as those being developed by ASCO—may be helpful. The plan must include not only the treatment choices, but also the methods for evaluating the effectiveness of treatment and complications of treatment.

Once the treatment plan is implemented, physicians should reassess and revise the personalized cancer care plan as needed. For example, oncologists must determine if there have been alterations in organ function or toxicity. Oncologists will also need to periodically re-evaluate the tumor and/or tumor markers, and determine whether there have been changes in characteristics of the tumor itself. This evaluation may require additional biopsies.

Lastly, personalized cancer care implies that there will be a preventive strategy to reduce the risk of new cancers in the patient and/or in the family based upon the personalized risk profiles established for the patient and, possibly, the patient's family. Risk assessment should be performed and genetic studies ordered if appropriate for the disease or syndrome. The oncologist will then have to decide about the individual patient's need for genetic counseling.

The core components of personalized cancer care follow-up can be found in Table 1 on page 20.

Personalized Cancer Care Predictive and Prognostic Tests

For many cancers, predictive and prognostic tests are now elements of standard care. Most often physicians are relying on the more established assays, but several newer tests can also be useful in decision making. Here are descriptions of predictive and prognostic tests available by disease site (see also Table 2 on page 21).

continued on page 20

ILLUSTRATION/NEIL BRENNAN

Although the usual treatment paradigm is initiation of a standard dose of a drug with subsequent adjustment based on toxicity, **newer strategies are available for certain drugs.**

Breast cancer. Personalized testing includes estrogen receptor and progesterone receptor analysis for decisions on hormone therapy. HER2 evaluation must be performed by immunohistochemistry (IHC) or preferably by FISH to determine the need for trastuzumab. Oncotype*DX* or MammaPrint testing determines the prognosis for recurrence and informs a decision on chemotherapy. BRCA1 and BRCA2 analysis modifies prognosis and the need for breast cancer surveillance and prevention in the patient and her family.

Non-small cell lung cancer. For NSCLC patients, mutations in the tyrosine kinase domain of EGFR have been important in determining whether to use specific agents such as erlotinib, chemotherapy, or both. In one study, survival of patients who harbored an EGFR mutation was superior with gefitinib initial therapy, compared to standard cytotoxic chemotherapy.[3] EGFR testing is recommended in all patients who could possibly have a mutation. (Mutations are more likely in never or light smokers, females, those with adenocarcinoma histology, or patients of Asian ethnicity.) Other possibly helpful analyses include B-RAF, K-RAS, and PIK3CA.

Soft tissue sarcomas. Evaluation of markers for gastrointestinal stromal cell tumors (GIST) should always be performed.[4] This includes CD117 and CD34. If CD117 is expressed, determination of mutation status may be predictive of imatinib sensitivity and the possible utility of other therapy such as sunitinib.[4]

Non-Hodgkin's lymphomas. Complete evaluation for T-cell and B-cell markers (including, of course, CD20) must be performed in each patient. This practice allows selection of individualized chemotherapy and/or biotherapy appropriate to the T or B cell origin of the tumor and expression of therapeutic targets such as CD20.

Myeloproliferative disease. In these patients, testing for the JAK-2 V617F mutation is important in selecting appropriate therapy and determining prognosis.[5]

Colorectal cancer. Determination of mutations in K-RAS or B-RAF assist in selecting appropriate patients for individualized use of anti-epidermal growth factor receptor monoclonal antibodies.[6] Patients with mutations do not respond to either cetuximab or panitumumab. Evaluation of microsatellite stability is useful both prognostically and predictively. Patients with instability (MSI-H) have a better survival (hazard ratio 0.65) even without adjuvant chemotherapy. Furthermore, MSI-H patients do not have improved survival after 5FU/leucovorin adjuvant chemotherapy. However, those patients do have a superior survival when receiving irinotecan with 5FU and leucovorin.[7] If a patient has MSI-H, further studies should be performed on blood samples to determine if the patient has germline mutations in HNPCC (hereditary non-polyposis colon cancer) genes to personalize the need for preventive therapy both in the patient and in the family.

Gastric adenocarcinoma. The finding of better results of chemotherapy with trastuzumab compared to chemotherapy alone in HER2 positive tumors indicates a possible need to perform HER2 testing in selected patients.[8] This decision depends on whether the payer will approve payment for trastuzumab if overexpression of the HER2 marker is identified.

Acute myelocytic leukemia. Determination of the individual's prognosis with genotype and molecular markers is

Personalized Cancer Care Follow-Up

Assessment of tumor response
- Routine markers
- Molecular analyses for minimal residual disease (e.g., CML)
- Circulating tumor cells
- Functional imaging (e.g., FDG PET)

Consideration for re-biopsy at tumor recurrence and/or progression

Determination of residual disabilities or reduced function
- Physical and/or functional
- Mental and/or cognitive
- Psychological (PTSD)
- Nutritional

Table 1. Elements of Comprehensive Personalized Cancer Care

- Plan surgery and/or biopsy to include performance of appropriate tests
- Review pathology to request additional appropriate tests
- Evaluate patient characteristics for therapeutic tolerance
- Conduct treatment planning
- Communicate the treatment plan to patient and his or her family
- Re-assess response and revise care plan as needed
- Carry out risk assessment and prevention
- Develop rehabilitation programs

The Patient from Hell: How I Worked with My Doctors to Get the Best of Modern Medicine and How You Can Too

An example of personalized follow-up for a patient is elegantly described in this book by lymphoma patient Stephen H. Schneider, PhD, (Da Capo Press: Cambridge, Mass. 2005). A member of the National Academy of Sciences, the author convinced his oncologist that detailed measurement of residual cancer cells by polymerase chain reaction (PCR) could help individualize his remission maintenance treatment decisions (which the oncologist did). This decision allowed the oncologist and patient to use Bayesian decision-making models based on sequential data feedback to adjust therapeutic plans.

In day-to-day practice, oncologists use this process to individually modify treatment decisions: cancer chemotherapy treatments are adjusted according to serial PET scans and tumor markers, and doses are adjusted according to toxicity and changing organ function.

ILLUSTRATION/ISTOCKPHOTO

Table 2. A Suggested Starting List of Personalized Cancer Care Laboratory Predictive and/or Prognostic Tests

Disease Site	Tests
Breast Cancer	ER, PR, HER2 Onco*type*DX, MammaPrint BRCA1, BRCA2
Lung Cancer (NSCLC)	EGFR, B-RAF, K-RAS
Soft Tissue Sarcoma	CD117, CD34
Non-Hodgkins Lymphoma	T, B-cell markers
Myelproliferative Disease	JAK2
Colorectal Cancer	K-RAS, B-RAF, MSI
Gastric Cancer	HER2
AML	Genotype, Flow cytometry markers
Pharmacology	CYP2D6, UGT1A1*28 DPD, Thymidylate synthase, 5FU levels
All Cancer Types	Chemoresponse tests Targets by IHC

important in planning induction chemotherapy as well as consolidation strategy for bone marrow transplantation.[9]

Drug therapy pharmacology. Personalized therapy is useful in drug therapy. Although the usual treatment paradigm is initiation of a standard dose of a drug with subsequent adjustment based on toxicity, newer strategies are available for certain drugs. Analysis of CYP2D6 polymorphisms in patients to be treated with tamoxifen may be able to indicate individuals who are poor metabolizers and who may require higher dosing of the drug or alternative hormonal therapy.[10] In patients who will be treated with irinotecan, detecting those with the UGT1A1*28 polymorphism can indicate patients who require dose reduction to prevent potentially fatal gastrointestinal toxicity.[11]

In determining the appropriate dose of 5FU, new technologies are available. Using a single steady state 5FU concentration to adjust subsequent cycles of 5FU infusional therapy results in improved response, reduced toxicity, and a trend to increased survival.[12] Pretreatment analysis of mutations in the rate-limiting catabolic enzyme dihydropyrimidine deydrogenase (DPD) and thymidylate synthase polymorphisms can detect individuals who require a reduction in 5FU dosing.[13]

New Tools for Personalized Cancer Care

In addition to the above tests, new tools have been developed to further support personalized cancer care. The first class of these is chemoresponse testing. A novel assay, developed at Vanderbilt University, determines chemotherapy induced apoptosis. The assay, called Microculture Kinetic or MiCK, has been well described.[14] Determining the phenotypic characterization of individual drug sensitivity is a predictive test analogous to assays that predict for sensitivity to bio-therapeutic treatment (for example, with trastuzumab or rituximab) and helps physicians determine the most appropriate chemotherapy for an individual patient. These results in acute myelocytic leukemia have indicated a correlation between high apoptosis in the assay and patient response and survival.[15] A marked survival advantage continues to be seen at seven years after MiCK testing and initial treatment if patients received chemotherapy that showed a higher degree of apoptosis in the assay.[16] In patients with ovarian cancer, the assay was able to identify and rank therapies from inactive to high activity.

Patients who were treated with chemotherapy that ranked best in the MiCK assay (as used by oncologists who

In the comprehensive evaluation and treatment of cancer patients,
it is important to realize that the additional work
cancer care **must be associated with adequate**

were blinded to the assay results) had a higher clinical benefit and a statistically significant longer survival compared to patients treated with non-best chemotherapy.[17] This chemoresponse assay has been applied to various cancers, including breast cancer, endometrial cancers, and others.[18,19] Additionally, there are older methods to determine chemotherapy drug resistance, which have been reviewed by ASCO and are still available for use.[20]

Thus, chemosensitivity testing is another useful tool for medical oncologists who are desirous of personalizing cancer care. Such testing enables the physician to choose the best and most effective treatments with less toxicity, resulting in better responses and improved survival.

Support Sources for Program Development and Implementation

Many resources are available to help community cancer centers and oncology practices establish a program in personalized cancer care. Here is a brief list of those resources.

1. The Association of Community Cancer Centers (ACCC). ACCC's journal, *Oncology Issues*, features articles related to technological advancements and their programmatic implications. Journal articles are archived online on the Members-only section of ACCC's website (*www.accc-cancer.org*). Sessions related to innovative new technologies and their programmatic implications are also included at ACCC's two national meetings. Meeting information is also available online.
2. Oncology State Societies. These societies are repositories for best practices in the implementation of personalized cancer care. Society administrators and officers, as well as Boards of Directors, can suggest methods for implementing these new programs.
3. National oncology meetings, such as those sponsored by ASCO, the America Society of Hematology (ASH), Community Oncology Alliance (COA), and the Oncology Congress.
4. The Administrators in Oncology Hematology Assembly (AOHA). Sponsored by the Medical Group Management Association (MGMA), AOHA is a forum for the exchange of information and ideas pertaining to the administration of oncology and hematology practices.
5. Cancer care consultants.
6. Pharmaceutical companies.

Identification of molecular targets by immunohistochemistry has been reported to be effective in selecting patients for appropriate chemotherapy. A recent study of chemotherapy selected by advanced IHC was shown to produce longer progression-free survival in 20 percent of patients compared to chemotherapy previously used.[21] Although some of these IHC assays require fresh tissue for analysis, many other individual tests can be performed on paraffin-fixed samples obtained prior to tumor progression.

Both chemoresponse assays and IHC target identification are tools that can help physicians with difficult management decisions, such as in drug-resistant relapsed patients. They can also help physicians select a therapy most likely to produce the best response and longer survival for patients who have several treatment options with historically similar results.

Implementing a Personalized Cancer Care Program

Community cancer centers and oncology practices that want to implement a personalized cancer care program must first identify local resources that are necessary for testing patients, including appropriate laboratory and pathology tests and molecular analyses, as well as IHC evaluations. This process usually requires discussions between the medical oncologist, pathologist, and payers to be certain that the cost of these tests is adequately covered.

Additionally, having an educational brochure or web-based online resource for patients that describes personalized cancer care and the tests, time, and insurance coverage necessary to provide the best treatment plan can be helpful. Personalized care usually requires longer pre-treatment time to develop the treatment plan, additional visits to discuss the personalized treatment options, and possibly additional co-payments for the necessary tests.

Because of the need for biopsies to obtain fresh tissue for certain immunohistochemical and especially cellular evaluations (such as chemoresponse testing), coordination between the medical oncologist and surgeons is important. To avoid multiple biopsies, surgeons need to review patients with the medical oncologist prior to surgical treatment, to determine if additional fresh tissue handling would be appropriate to personalize the care of the patient should a cancer be discovered. This practice has been done for many years with lymphoma analyses on lymph node biopsies, but now can be helpful for other solid tumors as well.

Administrative Implications

In the comprehensive evaluation and treatment of cancer patients, it is important to realize that the additional work required to implement personalized cancer care must be

required to implement personalized
reimbursement.

associated with adequate reimbursement. Discussion with payers about the need for additional testing is important to ensure that the community cancer center or oncology practice can represent the best interest of the patients in obtaining the most individualized and effective treatment care.

In addition, delivery of personalized cancer care may entail appropriate use of high-level codes that describe the complex visits necessary to:

- Obtain appropriate information
- Engage in comprehensive decision-making
- Discuss plans with patient and family
- Communicate and coordinate with other co-managing physicians.

Appropriate administrative changes must be incorporated within coding and billing procedures of the practice or community cancer center to be certain code usage accurately reflects the complex nature of personalized cancer care.

Cary A. Presant, MD, FACP, is past president of the Association of Community Cancer Centers. He has also served on the Board of Directors of the American Society of Clinical Oncology and is currently Chairman of the Board of the Medical Oncology Association of Southern California. He is a medical oncologist at Wilshire Oncology Medical Group in Los Angeles, Calif. Pat Whitworth, MD, FACS, is a surgical oncologist at Nashville Breast Center, Nashville, Tenn. Emery Salom, MD, is a gynecological oncologist at Palmetto General Hospital, Hialeah, Fla. Dirk Davidson, MD, is a medical oncologist at Cumberland Medical Center, Crossville, Tenn. Karl M. Rogers, MD, is a medical oncologist at Nashville Oncology Associates, Nashville, Tenn. Swapnil Rajurkar, MD, is staff physician and clinical investigator at Wilshire Oncology Medical Group, Los Angeles, Calif. Allan Hallquist, MD, is a director of pathology at DiaTech Oncology, Montreal, Canada.

Disclosures: Dr. Presant is a consultant to DiaTech Oncology and serves as Director of Medical Oncology. He receives grant support from DiaTech Oncology. Dr. Whitworth is a consultant to Genomic Health, Precision Therapeutics, DiaTech Oncology, and Veridex. He is on the speakers' bureau for Myriad. He receives grant support from DiaTech Oncology and Precision Therapeutics.

References

[1]Schilsky R. Personalizing cancer care: American Society of Clinical Oncology Presidential Address 2009. *J Clin Oncol.* 2009;27:3725-30.
[2]Steven Smith. Massachusetts General Hospital to Personalize Cancer Care. Boston Globe. March 3, 2009.
[3]Wu Y, Mok D, Chu B, et al. Evaluation of clinically selected patients with advanced non-small cell lung cancer recruited in China in a phase III randomized open label first line study in Asia of gefitinib versus carboplatin/paclitaxel (IPASS). *J Clin Oncol.* 2009;27:15s.
[4]Koh Y, Kim H, Lee H, et al. Kit and PDGFRA mutation status and the immunohistochemical expression profile of gastrointestinal stromal tumor patients treated with imatinib: seven-year single-center experience. *J Clin Oncol.* 2009;27:15s (abstract 10558).
[5]Zhan H, Spivak JL. The diagnosis and management of polycythemia vera, essential thrombocythemia and primary myelofibrosis in the Jak2 V617F era. *Clin Adv Hematol Oncol.* 2009;5:334-42.
[6]Souglakos J, Phillips J, Wang R, et al. Prognostic and predictive value of common mutations for treatment response and survival in patients with metastatic colorectal cancer. *Br J Cancer.* 2009;101:465-72.
[7]Bertagnolli MM, Niedzwiecki D, Compton CC, et al. Microsatellite instability predicts improved response to adjuvant therapy with irinotecan, fluorouracil and leucovorin in stage III colon cancer: Cancer and Leukemia Group B protocol 89803. *J Clin Oncol.* 2009;27:1814-21.
[8]Bang Y, Ching H, Xu J, et al. Pathological features of advanced gastric cancer: relationship to human epidermal growth factor receptor 2 (Her2) positivity in the global screening program of the ToGA trial. *J Clin Oncol.* 2009:27:15s,(abstract 4556).
[9]Bacher U, Haferlach C, Kern W, et al. Prognostic relevance of FLT3-TKD mutations in AML. The combination matters – an analysis of 3082 patients. *Blood.* 2008;111:2527-37.
[10]Schroth W, Goetz MP, Hermann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA.* 2009;302:1429-36.
[11]Liu C, Chen P, Chiou T, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer.* 2008;112:1932-40.
[12]Gamelin E, Delva R, Jacob J, et al. Individual fluorouracil dose adjustment based on pharmacokinetic follow up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. *J Clin Oncol.* 2008;26:2099-105.
[13]Schwab M, Zanger U, Marx C, et al. Role of genetic and nongenetic factors for fluorouracil treatment related severe toxicity. A prospective clinical trial by the German 5FU toxicity study group. *J Clin Oncol.* 2008;26:843-9.
[14]Kravtsov V, Fabian I. Automated monitoring of apoptosis in suspension cell cultures. *Lab Invest.* 1996;74: 557-570.
[15]Kravtsov V, Greer J, Whitlock J, Koury, M. Use of the microculture kinetic (MiCK) assay of apoptosis to determine chemosensitivities of leukemias. *Blood.* 1998;92:968-980.
[16]Koury M, Strickland S. Personal communication, manuscript in preparation 2009.
[17]Salom E, Penalver M. Personal communication, abstract submitted to ASCO, and manuscript in preparation, 2009.
[18]Whitworth P, Presant C, Rutledge J, et al. Chemosensitivity of patient breast cancer cells in vitro: correlation with prior chemotherapy and implications for personalized treatment planning. *J Clin Oncol.* 2009;27, 2009 (abstract 11563).
[19]Ballard K, Homesley H, Presant C, et al. In vitro chemosensitivity testing in endometrial carcinoma of single and combination chemotherapy using the novel microculture kinetic (MiCK) apoptosis assay: implications for endometrial carcinoma treatment. Abstracts, Western Association of Gynecological Oncology, 2009.
[20]Schrag D, Garewal H, Burstein H, et al. American Society of Clinical Oncology Technology Assessment: Chemotherapy sensitivity and resistance assays. *J Clin Oncol.* 2004;22:3631-8.
[21]Von Hoff D. Presented to the American Association for Cancer Research, 2009.