A Personalized Approach to Cancer Treatment: How Biomarkers Can Help

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BACKGROUND: The present approach to cancer treatment is often referred to as “trial and error” or “one size fits all.” This practice is inefficient and frequently results in inappropriate therapy and treatment-related toxicity. In contrast, personalized treatment has the potential to increase efficacy and decrease toxicity.

CONTENT: We reviewed the literature relevant to prognostic, predictive, and toxicity-related markers in cancer, with particular attention to systematic reviews, prospective randomized trials, and guidelines issued by expert panels. To achieve personalized treatment for cancer, we need markers for determining prognosis, predicting response to therapy, and predicting severe toxicity related to treatment. Among the best-validated prognostic markers currently available are serum concentrations of α-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) for patients with nonseminoma germ cell tumors and tissue concentrations of both urokinase plasminogen activator and plasminogen activator inhibitor 1 (PAI-1) for breast cancer patients. Clinically useful therapy predictive markers are estrogen and progesterone receptors to select patients with breast cancer for treatment with endocrine therapy and human epidermal growth factor receptor 2 (HER-2) to select breast cancer patients for treatment with trastuzumab (Herceptin). Markers available for identifying drug-induced adverse reactions include thiopurine methyltransferase (TPMT) to predict toxicity from thiopurines in the treatment of acute lymphoblastic leukemia and uridine diphosphate glucuronyltransferase to predict toxicity from irinotecan in the treatment of colorectal cancer.

CONCLUSIONS: Validated prognostic, predictive, and toxicity markers should help cancer treatment move from the current trial-and-error approach to more personalized treatment.

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The current approach to administering systemic therapy to cancer patients is largely empirical. As a result, some patients with aggressive disease may be undertreated, and some with indolent disease may be overtreated. In addition, for those patients who receive treatment, only a proportion derives clinical benefit, whereas adverse side effects are common. Most serious of all, a small number suffer from severe toxic effects, which in very rare cases may be fatal.

With recent developments in gene sequencing, targeted therapies, and molecular diagnostics, cancer treatment is beginning to move from the traditional “trial-and-error” approach to a position involving a personalized approach, i.e., giving the right drug at the right dose to the right patient. To achieve this situation, we need the following:

- Strong and independent prognostic markers that can reliably separate patients with indolent disease from those with aggressive forms. Patients with indolent disease may be able to avoid adjuvant chemotherapy, whereas those with aggressive disease are candidates for such treatment.
- Markers to prospectively predict response or resistance to specific therapies so that the right patients receive the right drugs.
- Markers to identify patients who are likely to develop severe toxic side effects from specific treatments.

The aim of this article is to review how advances in prognostic, predictive, and toxicity markers are leading to a personalized approach to cancer management.

Prognostic Markers

Prognostic markers have traditionally been defined as factors that predict disease outcome in the absence of systemic adjuvant therapy. Recently, however, the definition of a prognostic marker was modified to take into consideration the increasing number of patients with newly diagnosed malignancy who were receiving adjuvant systemic therapy. According to Sargent et al.
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(1), a prognostic marker can be defined as a factor that predicts outcome in the absence of systemic therapy or predicts an outcome different from that of patients without the marker, despite empiric therapy. A prognostic marker can thus differentiate patients into subgroups for which different treatment options, including the possibility of no treatment, are appropriate (1).

Traditional prognostic factors for malignancy include clinical and pathological criteria such as patient’s age, tumor size, tumor grade, and number of local lymph nodes with metastasis. Although these factors have been used for decades, they have limitations in predicting patient outcome (2). Consequently, in recent years, an enormous amount of research has been devoted to the study of new biological prognostic markers. Although hundreds of biological prognostic markers have been proposed in the last 2 to 3 decades, few have progressed to clinical use (see below).

Multiple problems bedevil published reports on biological prognostic factors in cancer (3, 4), including the following:

- Most studies were retrospective and used specimens that were readily available rather than representative of a clinically relevant group.
- Most studies contained small numbers of patients and were thus underpowered to see a true clinical effect.
- Results from many studies were not validated, especially in independent patient populations or prospective trials.
- In many studies, the prognostic impact of the putative marker was not shown to provide added benefit to that available from existing criteria.
- Most studies were carried out without written protocols, eligibility criteria, predetermined end points, or working hypotheses.
- In some studies, multiple end points and multiple subsets of patients were used, increasing the probability of chance statistically significant findings.
- Based on a literature search of studies describing the application of metaanalyses to cancer biological prognostic factors, Kyzas et al. (5) concluded that because of poor quality of design and reporting, many of the published studies might be unreliable.

Biological markers however, are potentially useful as prognostic indices in malignancy if they (6)

- Provide prognostic information additional to or independent of conventional prognostic factors.
- Provide stronger prognostic information than that available from conventional factors.
- Provide prognostic information within specific subgroups defined by traditional criteria, e.g., in lymph node–negative breast cancer or stage II colon cancer patients. In both these situations, biological prognostic markers may help in informed decision-making as to whether to administer or withhold adjuvant chemotherapy.

Even if all the above criteria are met, a new prognostic marker is unlikely to be used for clinical purposes unless its prognostic value has been validated in multiple independent studies, which ideally should include a prospective trial. Furthermore, a technically validated, robust, standardized, and cost-effective assay should exist for its measurement. Most importantly, the marker concentration or status must be able to affect patient management. Thus, in small hormone receptor–positive lymph node–negative breast cancer, a marker would be clinically useful if it could identify patients whose risk of relapse is so low that they could avoid having to receive adjuvant chemotherapy. Similarly, in stage II colon cancer, there is a need for markers capable of selecting those patients with aggressive disease that might benefit from adjuvant chemotherapy. Some of the best-validated cancer prognostic markers currently available are discussed below.

**SEER-BASED MARKERS**

Among the best-validated serum-based cancer prognostic markers are α-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) for patients with metastatic nonseminomatous germ cell tumors (NSGCTs). After a pooled analysis of data from >5000 patients, the International Germ Cell Cancer Collaborative Group established that pretreatment serum concentrations of AFP, hCG, and LDH were independent prognostic factors for patients with metastatic NSGCT (7). Pretreatment concentrations of these 3 markers were combined with specific clinical parameters (location of the primary and metastatic sites) to generate a new prognostic classification system for NSGCT (7).

This classification system is now widely used for patients with NSGCT in treatment decisions and selecting patients for clinical trials. Furthermore, it has been incorporated into both the American Joint Committee on Cancer (8) and the Union Internationale Contre le Cancer (UICC) staging systems for NSGCT (9). Currently, a number of expert panels such as

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4 Nonstandard abbreviations: AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NSGCT, nonseminomatous germ cell tumor; EGTM, European Group on Tumor Markers; HER-2, human epidermal growth factor receptor 2; uPA, urokinase plasminogen activator; PAI-1, plasminogen activator inhibitor 1; ASCO, American Society of Clinical Oncology; ER, estrogen receptor; RS, recurrence score; PR, progesterone receptor; ADR, adverse drug reaction; TMPT, thioptine methyltransferase; UGT1A1, uridine diphosphate glucuronyltransferase 1A1.
the European Group on Tumor Markers (EGTM) (10) and the National Academy of Clinical Biochemistry (NACB) in the U.S. (11) recommend the use of AFP, hCG, and LDH for determining prognosis in patients with NSGCT.

Other serum-based markers that may be useful in determining prognosis include prostate-specific antigen (PSA) in prostate cancer (12), carcinoembryonic antigen (CEA) in colorectal cancer (13), cancer antigen (CA) 125 in ovarian cancer (14), and CA 15-3 in breast cancer (15).

TISSUE-BASED MARKERS

HER-2 in breast cancer. Although serum is more readily available than tumor tissue, most research into cancer prognostic markers has focused on tissue rather than serum. This applies particularly for breast cancer. One of the most widely investigated tissue-based prognostic markers in breast cancer is human epidermal growth factor receptor 2 (HER-2). In 2003, after a review of the literature, Ross et al. (16) identified 81 studies, involving >27 000 patients, that related HER-2 status to patient outcome. Although most of the reports used a nonstandardized immunohistochemical method to measure HER-2, a variety of other assays were also used including Western blotting, Southern blotting, and fluorescence in situ hybridization (FISH). No attempt was made to obtain individual results or combine data from the different studies.

Of the 81 studies identified, 73 (90%) found that either HER-2 gene amplification or HER-2 protein overexpression predicted patient outcome using either univariate or multivariate analysis. In 52 of the 73 studies (71%) that used multivariate analysis, the adverse prognostic impact of HER-2 was independent of traditional prognostic factors. A minority of studies however, reported no significant association between HER-2 and patient outcome.

In their literature review, Ross et al. (16) did not discriminate between breast cancer patients with lymph node–positive and lymph node–negative disease. It should thus be pointed out that whereas most publications reported a significant correlation between HER-2 and patient outcome in node–positive disease, the prognostic impact of the protooncogene in lymph node–negative patients, especially in those not receiving systemic therapy, is less clear (17).

Despite this limitation, a number of expert groups including the St Gallen Consensus Conference (18), EGTM (19), and NACB (11) panels recommended that HER-2 status be used in combination with other factors for risk classification of newly diagnosed breast cancer patients. The American Society of Clinical Oncology (ASCO), however, did not recommend the use of HER-2 for determining prognosis in newly diagnosed breast cancer patients (20).

Urokinase plasminogen activator and PAI-1 in breast cancer. Two of the best-validated prognostic biomarkers in breast cancer are the serine protease, urokinase plasminogen activator (uPA), and its endogenous inhibitor PAI-1 (plasminogen activator inhibitor 1). For breast cancer patients with lymph node–negative disease, the prognostic impact of these 2 proteins has been validated using both a multicenter randomized prospective study and a pooled analysis of raw data (21, 22). uPA and PAI-1 are thus among the best-validated biological prognostic factors for breast cancer, having undergone validation in studies with the 2 highest levels of evidence (i.e., level of evidence type 1) (23).

uPA and PAI-1 are thus potentially useful in selecting lymph node–negative breast cancer patients who may be able to avoid the side effects and costs of adjuvant chemotherapy. Currently, EGTM (19), NACB (11), and ASCO (20) panels support the use of uPA and PAI-1 for determining prognosis in newly diagnosed breast cancer patients, especially those with lymph node–negative disease. According to the ASCO guidelines, newly diagnosed breast cancer patients with low concentrations of uPA and PAI-1 have such a low risk of recurrence, especially in those with hormone receptor–positive tumors who will receive adjuvant hormone therapy, that chemotherapy will contribute only minimal benefits (20).

Multigene signatures. Some of the most potent prognostic information for cancer patients has been obtained using multiparameter assays, e.g., by measuring multiple mRNA species using either gene expression arrays or multiplex RT-PCR assays. Indeed, multigene signatures have now been reported to provide prognostic information in patients with most types of tumors. However, the validity of many of these findings have been questioned (24). Dupuy and Simon (24) reviewed published microarray studies and concluded that many contained basic flaws relating to methodological errors occurring in the statistical analysis of the relationship between gene expression findings and patient outcome. Such problems are more prevalent when analyzing large numbers of variables using relatively small numbers of patients. To minimize these problems in future work, the authors proposed guidelines for statistical analysis relating to clinical microarray work (24).

Two main approaches have been used for measuring the expression of multiple genes, gene expression microarray and multiplex PCR.

Gene expression microarray. One of the best-studied gene signatures is the 70-gene profile originally identi-
fied by van’t Veer et al. (25) for predicting outcome in newly diagnosed breast cancer patients. In a pilot study, these authors used DNA microarray to measure the expression of approximately 25 000 genes in archival tumors from 78 patients with lymph node–negative breast cancer <55 years of age. The expression of 231 genes was significantly correlated with the formation of distant metastasis within 5 years of diagnosis. A core set of 70 of these genes predicted the development of metastasis in 65 (83%) of these patients, with only 5 poor prognostic and 8 good prognostic signatures incorrectly classified. Application of this signature to an independent group of 19 breast cancer patients yielded only 2 incorrect classifications.

The prognostic value of this signature was subsequently validated in a partially independent group of 295 lymph node–negative and –positive patients from the same institution (26). In this validation study, the probability of remaining free of distant metastasis at 10 years postsurgery was 85.2% in the patients with the good signature and 50.6% in those with the poor signature. The estimated hazard ratio for distant metastasis in the patients with the poor prognostic signature compared with the group with the good prognostic signature was 5.1 (95% CI 2.9–9.0, P < 0.001). A similar significant difference in outcome between patients with the good and poor signature was found in patients with lymph node–negative disease. Multivariate analysis showed that the gene signature was an independent predictor of disease outcome and was more potent than standard criteria.

More recently, this gene signature was validated in an independent set of 302 node–negative patients from 5 European centers who had not received systemic adjuvant therapy (27). Again, the 70-gene signature performed better than standard clinicopathological criteria for predicting outcome. In this study, the utility of the gene signature was compared with the widely used Adjuvant! Online prediction system (based on classic clinical-pathological factors). For the patients with discordant risk classification, the gene signature was a more accurate predictor of outcome than the clinical-pathological model. A commercial test based on this gene profile, known as MammaPrint, has been made available by Agenda.

Currently this 70-gene signature is undergoing prospective validation as part of the Microarray for Node-negative Disease Avoids Chemotherapy (MINDACT) trial (28). This trial plans to enrol approximately 6000 lymph node–negative breast cancer patients. Risk assessment will be carried out using both the 70-gene signature and standard clinicopathological factors. The main objective of this trial is to confirm that lymph node–negative breast cancer patients with low risk of recurrence based on the above gene signature, but at high risk based on clinicopathological factors, can be safely spared adjuvant chemotherapy without affecting distant metastasis-free survival.

In 2007, MammaPrint was cleared by the U.S. Federal Drug Administration (FDA) for determining prognosis in breast cancer patients <61 years of age with stage I or stage II disease, tumors 5 cm or less in size, and lymph node–negative disease. For determining prognosis, MammaPrint should be used only in combination with other clinicopathological factors.

Multiplex RT-PCR. The best-known prognostic multiplex RT-PCR signature is the Oncotype DX test (Genomic Health). This test uses multiplex RT-PCR to measure the expression of 21 genes (16 cancer-associated and 5 control genes) and was originally investigated for its ability to predict the risk of distant metastases in lymph node–negative estrogen receptor (ER)-positive breast cancer patients receiving adjuvant tamoxifen (29). These predictive genes were selected from approximately 250 candidate genes previously reported from the published literature, databases, and gene expression microarray findings. The final 16 were chosen on the basis of their association with disease recurrence in 3 preliminary studies.

A recurrence score (RS) algorithm was developed that predicted low, intermediate, and high risk of distant metastasis for patients receiving 5 years of adjuvant tamoxifen. The RS was subsequently validated prospectively in 668 women with ER-positive and lymph node–negative breast cancer treated with adjuvant tamoxifen in the National Surgical Adjuvant Bowel and Breast (NSABP) B-14 trial. Based on the RS, 338 (51%) of the patients were found to have low risk of recurrence, 22% had intermediate risk, and 27% had high risk. Multivariate analysis showed that the hazard ratio of the RS was 2.81 (95% CI 1.70–4.64, P < 0.001).

As well as predicting outcome in patients treated with adjuvant tamoxifen, the RS was found to be associated with benefit from adjuvant chemotherapy (30). This study involved 651 patients of whom 227 were randomly assigned to tamoxifen and 424 randomly assigned to receive chemotherapy plus tamoxifen. Patients with a high RS were found to benefit from chemotherapy (relative risk of recurrence, 0.26), whereas those with low RS derived little, if any, benefit. Patients with intermediate RS also did not appear to derive a major benefit but further research is required to confirm this.

Based on the above findings, women with low RSs might be expected to derive little benefit from adding adjuvant chemotherapy to hormonal therapy, i.e., the benefits may not exceed the risks. On the other hand, those with a high RS would be expected to gain from the combined treatment, compared to the risks (30).
As mentioned above, for those patients with intermediate RSs, further work is required. Such a study is currently in progress as part of the Trial Assigning Individualized Options for Treatment (TAILORx) (31).

This trial aims to enroll >10 000 lymph node–negative women with ER- and/or progesterone receptor (PR)-positive and HER-2–negative breast cancer. Patients will be allocated to one of 3 groups based on the RS, a low-risk group with a score <11, a medium-risk group with a score 11–25, and a high-risk group with a score >25. Women in the low-risk group will be given hormone therapy, and those in the high-risk group will receive chemotherapy followed by hormone therapy. Patients with intermediate RS will be randomized to receive hormonal therapy alone or hormone therapy plus chemotherapy. The primary aim is to establish if adjuvant chemotherapy improves survival in the group with the intermediate score.

According to the ASCO guidelines (20), the Oncotype DX test can be used to predict the risk of recurrence in patients treated with tamoxifen; in particular, the test may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. A particular advantage of the Oncotype DX test over most other existing multigene profiles is that it can be carried out on formalin-fixed and paraffin-embedded tissue, thus allowing the use of archival tissue.

Although the MammaPrint and Oncotype DX profiles are the best-validated prognostic genes signatures, several other multigene prognostic profiles have been described. Indeed, prognostic gene signatures have now been reported for most types of malignancy (for review, see (32)).

Proteomics. In contrast to studies measuring multiple mRNA species, the use of proteomics or multiple proteins to predict patient outcome has so far been disappointing. Most of the studies reported to date have been preliminary, and few if any have undergone external validation. With the development of more robust technologies, it would be expected that proteomics will make a significant future contribution to both prognosis and therapy prediction.

**Predictive Markers**

Therapy predictive markers guide the choice of treatment (33). Patients with marker levels indicating a likely response to a specific therapy are clearly candidates for undergoing treatment with that therapy. On the other hand, those patients unlikely to benefit could receive an alternative therapy that may be more beneficial. In the absence of an effective alternative therapy, they could volunteer to participate in clinical trials or they could make an informed decision to avoid the needless costs and toxicity of likely ineffective therapy. The availability of predictive markers clearly allows for more efficient and cost-effective patient treatment.

Predictive markers are more difficult to evaluate than prognostic markers. This applies especially in the adjuvant setting, where measurable disease is not present. Ideally, in this setting, markers should be investigated as part of randomized prospective trials comparing the effects of treatment with a control group receiving no adjuvant therapy. Such trials require large numbers of patients and long-term follow-up. Compared to the adjuvant situation, predictive markers can be more easily and quickly evaluated in either the neoadjuvant or metastatic disease setting. In both these situations, objective tumor response can be directly measured using established response criteria. For the metastatic setting, these include response rate, time to progression, survival, and risk of toxicity (1). In the neoadjuvant setting, the primary end point is pathological evidence of response. Sargent et al. (1) have published potential trial designs for the evaluation of single predictive markers.

Currently, only 3 oncological predictive markers are in widespread clinical use—ER, PR, and HER-2. ER and PR are used for selecting women with breast cancer for endocrine therapy, and HER-2 is used for identifying women likely to respond to specific anti–HER-2 therapies, especially trastuzumab.

**ER and PR for Predicting Response to Hormone Therapy in Breast Cancer**

The prototype predictive marker in oncology is ER, i.e., ER-α, which is used in selecting for likely response to hormone therapy in patients with either early or advanced breast cancer (34). Although originally used for predicting response to hormone therapy in advanced breast cancer, ER is currently mostly used for predicting benefit from tamoxifen and aromatase inhibitors in patients with early breast cancer (34).

Although the negative predictive value of ER is high because ER-negative patients almost never benefit from hormone therapy, its positive predictive value is less accurate. For example, adjuvant tamoxifen significantly reduces the risk of recurrence in ER-positive patients, but approximately 40% of such patients eventually relapse due to intrinsic or acquired resistance (35). Clearly, additional predictive markers for hormone therapy are necessary to achieve personalized treatment.

PR is induced by estrogen acting via the ER. PR was thus hypothesized to be a marker for a functional ER (36). Consistent with PR being a marker for an active ER, the combined presence of both receptors has
been shown to be more reliable for predicting benefit from hormone therapy than the presence of ER alone (37).

HER-2 FOR PREDICTING RESPONSE TO DIFFERENT THERAPIES IN BREAST CANCER

Anti-HER-2 therapies. Currently, the main clinical use of HER-2 is for predicting response to trastuzumab (Herceptin) (38). Trastuzumab is a monoclonal antibody directed against the extracellular domain of HER-2. In HER-2–positive patients with advanced breast cancer, trastuzumab monotherapy induced tumor regression in 12%–34% of patients for a median duration of 9 months (38). When administered with chemotherapy to patients with advanced breast cancer, response rates >50% have been found (38). When given concurrently or sequentially with chemotherapy to patients with HER-2–positive early breast cancer, trastuzumab was shown to reduce the risk of recurrence by approximately 50%.

Preclinical experiments established that overexpression of HER-2 was necessary for the murine precursor of trastuzumab, i.e., antibody 4D5, to inhibit tumor growth (39). Consistent with these findings, published clinical studies concluded that benefit of trastuzumab was found exclusively in patients with breast cancer that overexpresses or amplifies the HER-2 gene (37). Patients lacking HER-2 gene amplification or overexpression have not been shown to benefit from trastuzumab, although this has not been rigorously tested. The prevailing view, however, is that trastuzumab should be given only to breast cancer patients whose tumor exhibits HER-2 gene amplification or overexpression of the HER-2 protein as determined by a validated assay.

Whereas trastuzumab is currently the most widely used therapy targeted to HER-2, several other anti-HER-2 agents are undergoing clinical trials (for review, see (40)). These include the monoclonal antibody pertuzumab, which prevents HER-2 from interacting with the other HER family members, and tyrosine kinase inhibitors, such as lapatinib, that inhibit both EGFR and HER-2 (40). Emerging data suggest that HER-2 gene amplification/overexpression is necessary for efficacy from lapatinib (41).

Other therapies. Several small-scale studies in which HER-2 was determined retrospectively suggest that amplification/overexpression of this protooncogene is associated with relative resistance to adjuvant tamoxifen (for review, see (33)). On the other hand, amplification/overexpression appears to be associated with a preferential response to anthracycline-based adjuvant therapy (33). In a recent pooled analysis of 8 randomized trials comparing adjuvant anthracycline vs non-anthracycline-based regimens in the treatment of early breast cancer, Gennari et al. (42) found that in HER-2–positive patients (n = 1536), anthracyclines were superior to nonanthracycline-based therapy using both disease-free interval and overall survival as end points. In contrast, in HER-2–negative patients (n = 3818), anthracyclines failed to improve disease-free interval or overall survival. This study suggests that the benefit of adjuvant anthracycline therapy in early breast cancer is confined to women with HER-2–positive tumors. Measurement of HER-2 status may thus be used for

Table 1. Potential markers for predicting response or resistance to specific cancer therapies.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Malignancy</th>
<th>Drug</th>
<th>Disease setting</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT&lt;sup&gt;a&lt;/sup&gt; (gene methylation status)</td>
<td>Glioma</td>
<td>Alkylating agents</td>
<td>Neoadjuvant/adjuvant</td>
<td>(43–46)</td>
</tr>
<tr>
<td>TOP2A (gene amplification)</td>
<td>Breast</td>
<td>Anthracyclines</td>
<td>Adjuvant</td>
<td>(47, 48)</td>
</tr>
<tr>
<td>EGFR (specific mutations)</td>
<td>Lung</td>
<td>Gefitinib and Erlotinib</td>
<td>Advanced</td>
<td>(49–52)</td>
</tr>
<tr>
<td>Tau</td>
<td>Breast</td>
<td>Paclitaxel</td>
<td>Neoadjuvant</td>
<td>(53–55)</td>
</tr>
<tr>
<td>Gene microarray</td>
<td>Breast</td>
<td>Polychemotherapy</td>
<td>Neoadjuvant</td>
<td>(56–59)</td>
</tr>
<tr>
<td>KIT (specific mutations)</td>
<td>GIST</td>
<td>Imatinib</td>
<td>Metastatic</td>
<td>(60, 61)</td>
</tr>
<tr>
<td>KRAS mutations</td>
<td>Colorectal</td>
<td>Cetuximab and panitumumab</td>
<td>Metastatic</td>
<td>(62–65)</td>
</tr>
<tr>
<td>Gene microarray</td>
<td>ALL</td>
<td>Prednisolone, vincristine, l-asparaginase, daunorubicin</td>
<td>Newly diagnosed</td>
<td>(66)</td>
</tr>
</tbody>
</table>

<sup>a</sup> None of the markers listed are currently in widespread clinical use. GIST, gastrointestinal stromal tumor; ALL, acute lymphoblastic leukemia.

<sup>b</sup> Human genes: MGMT, O-6-methylguanine-DNA methyltransferase; TOP2A, topoisomerase (DNA) II alpha 170kDa; EGFR, epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian); KIT (alias c-KIT), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog.
EMERGING PREDICTIVE MARKERS

Other potential oncological predictive markers are listed in Table 1. None of these markers are currently in widespread clinical use. Furthermore, it is unclear whether most of these are true predictive markers, prognostic markers, or a combination of both.

Markers for Predicting Severe Drug-Associated Toxicity

Serious adverse drug reactions (ADRs) have been defined as any untoward medical occurrence that results in death, requires hospital admission or prolongation of existing hospital stay, results in significant disability/incapacity, or is life threatening (67). Anticancer drugs are particularly noted for their adverse toxic side effects (43). As with therapy predictive markers, clearly it would be desirable to prospectively identify those patients who are likely to suffer from serious ADRs. At present, only 2 markers are available for this purpose, thiopurine methyltransferase (TMPT) for predicting toxicity from thiopurines and UDP-glucuronosyltransferase 1A1 (UGT1A1) for predicting toxicity from irinotecan (Camptosar). A further marker, dihydropyrimidine dehydrogenase (DPD), is undergoing evaluation for predicting toxicity from 5-fluorouracil (5-FU) but is not yet ready for clinical application.

TPMT FOR PREDICTING TOXICITY FROM THIOPURINES

Thiopurines such as 6-mercaptopurine, 6-thioguanine, and azathioprine are prodrugs used to treat acute lymphoblastic leukemia as well as certain benign diseases (e.g., inflammatory bowel disease and rheumatoid arthritis). The anticancer actions of thiopurines are mediated via inhibition of the formation of nucleotides necessary for DNA and RNA synthesis. These drugs are converted to 6-thioguanine nucleotides, in a reaction catalyzed by TMPT (68). Because TMPT is the primary inactivating enzyme for thiopurines, subjects with decreased activity accumulate high concentrations of the active thioguanine when treated with standard doses of the prodrug (68). This can result in severe and life-threatening hematopoietic toxicity.

The TMPT gene has been shown to exhibit at least 9 variable alleles in white populations (68,69). Most cases of decreased TMPT activity have been found in patients with 3 of these alleles, TPMT*2, TPMT*3A, and TMPT*3C. Subjects heterozygous for these alleles have intermediate activity, whereas those homozygous are TMPT deficient. Subjects that are compound heterozygotes (e.g., TPMT*2/TPMT*3A and TPMT*3A/TMPT*3C) also lack the transferase (68,69).

In the populations studied to date, approximately 90% of subjects have high activity of TMPT, 10% have intermediate activity, and 0.3% have little or no detectable activity (69). Multiple studies have shown that subjects with TMPT deficiency are at high risk of developing hematopoietic toxicity if given standard doses of thiopurines. In addition, subjects who are heterozygotes have an intermediate risk of dose-limiting toxicity, whereas those with 2 copies of the wild-type gene can receive the standard dose (69).

Assays for TMPT genotyping have been available for >10 years and have been shown to be cost-effective in certain clinical settings (70). The main reason for measuring TMPT status is to detect subjects with little or no activity. These patients may be able to avoid exposure to potentially fatal treatment with thiopurines. Measurement of TMPT status provides one of the best examples currently available for predicting severe toxicity from an anticancer agent. Indeed, according to Sanderson et al. (70), it would now be difficult to defend a deficient TMPT-related fatality, especially in the treatment of chronic diseases that are generally not life-threatening.

UDP-UGT1A1 FOR PREDICTING TOXICITY FROM IRINOTECAN

Irinotecan is used in the treatment of several cancer types, especially metastatic colorectal cancer (CRC). Activation requires conversion to 7-ethyl-10-hydroxycamptothecin (SN-38), a reaction catalyzed by the carboxylesterase (CES), CES2. SN-38 exerts its anticancer effects via inhibition of topoisomerase 1. SN-38 is further conjugated and detoxified following glucuronidation in the presence of uridine diphosphate glucuronyltransferase 1A1 (UGT1A1) (71).

The UGT1A1 promoter contains between 5 and 8 TA repeats, the 6-repeat allele being the most common. An inverse relationship exists between the number of repeats and expression of the enzyme. The presence of 7 repeats rather than the usual 6 gives rise to a variant allele known as UGT1A1*28. The UGT1A1*28 allele results in reduced UGT1A1 expression, which in turn leads to reduced SN-38 glucuronidation (71).

Multiple studies have shown that subjects with the homozygous UGT1A1*28 gene are at increased risk of developing leucopenia and severe delayed-type diarrhea following treatment with irinotecan (71). A recent metaanalysis, however, concluded that hematologic toxicity was confined to patients given medium and high doses of irinotecan and not to those who received low doses (72). Measurement of the UGT1A1*28 genotype may thus be useful in predicting severe toxicity from irinotecan, especially after the administration of medium and high doses (72). In 2005, the FDA cleared a specific test for determining UGT1A1 gene status. However, the decision to perform UGT1A1*28 genetic
testing before the administration of irinotecan was left to the discretion of the treating physician.

**Implication of Personalized Treatment**

The practice of personalized treatment for cancer will have major implications for pharmaceutical companies, diagnostic companies, health care providers, and patients. For pharmaceutical companies, it may result in the demise of the “blockbuster” drug, i.e., a drug with $1 billion or more annual sales. On the other hand, the availability of predictive markers should result in having enriched populations for participation in clinical trials (73). This in turn should reduce the cost and time of trials. In addition, the availability of toxicity markers should limit the number of ADRs and thus save pharmaceutical companies from possible litigation and the risk of having to withdraw drugs from the market (73).

For diagnostic companies, personalized treatment will require a major change in emphasis. Traditionally, these companies have focused on serum-based screening and monitoring markers. To become involved in the personalized treatment of cancer, an expanded test menu that includes prognostic, predictive, and toxicity markers will be necessary. This will demand the production of tissue-based as well as blood-based tests. Collaboration with academic researchers and pharmaceutical companies may be necessary to achieve these ends.

The biggest beneficiary of personalized medicine should be the patient. With personalized medicine, the probability of a positive response should be enhanced, as therapy will be given only to those who are likely to benefit. At the same time, the likelihood of adverse toxic side effects should be substantially reduced, as therapy should not be administered to those that do not require it or to those who are increased risk of suffering from adverse reactions. This increased efficacy should also result in overall reduced costs for health care providers (73–75).

**Conclusion**

As of now, personalized treatment for cancer is only beginning, with a small number of validated drug-test companion products available (76). Currently, personalized treatment is most advanced for breast cancer. For this malignancy, we have tests such as ER, uPA/PAI-1, HER-2, Oncotype DX, and MammaPrint to personalize treatment decisions. Similar tests are likely to be available for other cancers in the future. The evolution of personalized treatment is likely to be slow. However, the ultimate aim should be to have personalized treatment for every patient with cancer. Achieving this aim will require a multidisciplinary effort involving clinical chemists, clinical molecular biologists, clinical pharmacologists, molecular pathologists, pharmaceutical companies, and diagnostic companies. Surely, the move toward the personalized treatment of patients with cancer should be one of the most laudable goals of academic cancer researchers, pharmaceutical companies, and diagnostic companies.

**References**


